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A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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The Journal of Pediatrics

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Original Communications

ADRENAL INSUFFICIENCY IN INFANCY

A CLINICAL CLASSIFICATION, REVIEW, AND A REPORT OF A CASE

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MEDICAL CORPS, UNITED STATES ARMY

ONE HUNDRED years ago, Thomas Addison[1] first reported the clinical and pathologic descriptions of the disease which bears his name. His classical contribution has been augmented by numerous clinical reports published during the past century, and especially by the physiologic and chemical observations reported during the past fifteen years. The bulk of our knowledge concerning the functions of the adrenal cortex has been obtained by clinicopathological studies of patients with abnormal conditions of the adrenal cortex. Most of these cases have occurred in adults. The natural history of adrenal insufficiency in infancy is not so well documented.

In a critical review of the literature published in 1946, Jaudon[2] found only sixty-two proved cases of Addison's disease in children under the age of 15 years. Only four of these cases were in children under the age of 5 years. This small number of "the experiments of nature" has offered little opportunity for clinical investigation.

In all the reported cases of adrenal insufficiency in infancy there has been an associated element of intersexuality. The purpose of this paper is to contribute the results of our studies of a case of adrenal insufficiency followed from birth until death. Our patient lived for twenty months. We believe this to be the first reported case of pure adrenal insufficiency in infancy. The primary physiologic failure exhibited by this patient was a deficiency of the "S" factor. Our patient exhibited no evidence of abnormal differentiation of the urogenital ridge. A report of post-mortem findings is included.

Considering the difference between the size and histologic appearance of the adrenal cortex in the newborn infant and that in the adult, it seems inevitable that eventually a case should occur in which the normal transition should fail to take place. Cases have been described in which the normal progression of development was arrested with a persistence of the "fetal cortex." We believe the case we are about to present to be the first in which normal resolution of the "fetal cortex" evidently occurred but complete development of

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Read before the Texas Pediatric Post-Graduate Conference, Baylor University Medical School, Houston, Texas, April, 1949.

the normal adult type of cortex seems to have been held in abeyance. Although this may have been the end result of hemorrhage into the adrenal cortex during the neonatal period, we believe that it represents *hypoplasia of the adrenal cortex.*

CASE REPORT

This patient, D. S., was born at Brooke General Hospital Dec. 20, 1946. He died at the same hospital on Aug. 19, 1948, at the age of 20 months. The mother had a stormy pregnancy, but delivery was not complicated. The patient's parents and two siblings are living and well. There was no history of hereditary or familial disease.

The present illness dates from birth, because following discharge from the nursery this infant became a feeding problem. Vomiting resembling that found in pyloric stenosis developed and persisted for six months. He had a few loose stools but never frank diarrhea. On one occasion, at the age of 4 months, the patient "lost consciousness" for a period of fifteen minutes. His weight at that time was 12 pounds, 8 ounces. He appeared rather pale and undernourished but was not acutely ill. The temperature was normal. He was admitted to the hospital for forty-eight hours at this time. Routine studies were within normal limits.

When the patient reached 6 months of age he was 26 inches long and weighed 13 pounds, 13 ounces. He had consistently traveled channel A-7 on Wetzel's "Baby Grid," but had only reached level 85. He should have reached level *65.* No diagnosis having been made, the patient was admitted to the hospital where a careful search was made for congenital anomalies.

Physical examination at this time revealed a happy, playful 6-month-old infant whose developmental quotient (Gesell) was normal. The only physical finding of note was a peculiar golden "tanned" appearance of the skin. Rather thorough laboratory investigations of the body systems were within normal limits. No clues having been obtained, the patient was again discharged. For the next two months he did fairly well on lactic acid milk. Vomiting ceased.

He was readmitted at 8 months of age on Sept. 15, 1947, because of an acute illness characterized by chills, fever, and vomiting of twenty-four hours' duration. Physical examination was essentially negative except for some increase in the pigmentation previously noted. It had become definitely black on the back of his hands and over the extensor surfaces of the feet. Jaudon[3] described similar pigmentation in an infant known to have adrenal insufficiency. Blood urea nitrogen was 33 mg. per cent and carbon dioxide was 29 volumes per cent. Two days later, despite parenteral fluids, the carbon dioxide was still only 33 volumes per cent. On the fourth hospital day the patient developed roseola infantum. An intensive effort to substantiate the diagnosis of adrenal insufficiency was made at this time.

Laboratory Investigation.—Laboratory tests showed the following: an icterus index of 3; blood protein 5.82 Gm. per cent; cholesterol 156.2 mg. per cent; blood urea nitrogen, 15 mg. per cent; blood sugar 73 mg. per cent; carbon dioxide 33 volumes per cent; serum sodium 312.3 mg. per cent; serum potassium 22.5 mg. per cent; serum calcium 11.4 mg. per cent; serum magnesium 2.2 mg. per cent; serum phosphorus 5.9 mg. per cent; 17-ketosteroids 0.12 mg. per twenty-four hours; methemaglobin 0.04 mg. per cent. Results of oral glucose tolerance tests (1.75 Gm. per kilogram of body weight) were: fasting 64 mg. per cent, one-half hour 71.5 mg. per cent, one hour 73.5 mg. per cent, two hours 68.0 mg. per cent, three hours 63.5 mg. per cent. Results of intravenous glucose tolerance test (1.0 Gm. of glucose per kilogram of body weight) were: fasting 78 mg. per cent, one-half hour 129 mg. per cent, one hour 115 mg. per cent, two hours 76 mg. per cent, three hours 69.6 mg. per cent. Insulin tolerance (0.25 unit per kilogram of body weight) was: fasting 41.3 mg. per cent, one-half hour 34.0 mg. per cent, one hour 29.8 mg. per cent, two hours 34.2 mg. per cent. Mild convulsions occurred at this time so the test was discontinued. Epinephrine tolerance (0.5 c.c. epinephrine given) showed: fasting 43.5 mg. per cent, one-

half hour 74.2 mg. per cent, one hour 39.9 mg. per cent. X-rays of the skull, chest, and long bones were interpreted as normal. Kidney-ureter-bladder films and intravenous pyelogram were normal. First and second strength tuberculin tests were negative.

Although most observers were convinced at this time that the patient had Addison's disease, no therapy was begun. The patient was followed in the outpatient clinic. He then began to make steady progress. In the next four months he advanced 45 level lines on the Wetzel Baby Grid. At 10 months of age he was 28 inches tall and weighed 20 pounds, 8 ounces. By the age of 13 months he had completely overcome his developmental lag. He weighed 25 pounds and was 30 inches tall. Had he been receiving substitution therapy the results would have been considered excellent.

On Jan. 28, 1948, at the age of 13 months, the patient was readmitted because his mother had tried to awaken him but could not do so. Every few minutes he had a severe generalized convulsion. On the night before admission, vomiting, mild diarrhea, and slight elevation of temperature had been noted. When seen in the hospital the patient was comatose and he had had about six generalized convulsions during a period of two hours. On examination the eye, ear, nose, throat, chest, and abdomen were negative. The skin was dry and showed almost black pigmentation. He was somewhat dehydrated. The pulse was thready and about 90 per minute. The heart sounds were faint but no murmurs could be heard. Blood pressure could not be auscultated, but a systolic pressure could be palpated at 70. Kernig's sign was negative and deep reflexes were not abnormal. There was no nuchal rigidity. During one of the convulsions the patient had a large, very foul smelling, watery, green stool. Blood was drawn for study. The patient was then given 250 c.c. of glucose in saline intravenously. Before the injection was completed he awoke, noticed his surroundings, and began to cry. He was given 5 c.c. of adrenal cortical extract (Eschatin—Parke, Davis & Co.) intramuscularly. This was repeated at three-hour intervals. After the intravenous fluids were given his blood pressure was 100/60. Three hours later he was sitting up and taking fluids orally.

In addition to adrenal cortical extract he was started on daily doses of 1 c.c. (5 mg.) of desoxycorticosterone acetate subcutaneously and 200 c.c. of normal saline orally, daily. For three days he was listless and vomited occasionally. He then recovered and seemed to be a perfectly normal infant.

Laboratory Investigations on Admission (Patient in Coma).—Laboratory tests showed: total base 131 meq. per liter; blood urea nitrogen 25 mg. per cent; blood sugar 29 mg. per cent; chloride (as sodium chloride) 513 mg. per cent; carbon dioxide 41 volumes per cent; sodium 271.2 mg. per cent; potassium 24.5 mg. per cent; calcium 9.1 mg. per cent. Blood cultures were negative. Spinal fluid was negative, except for a sugar of 25 mg. per cent. Stool cultures were negative. Catheterized urine showed 2 plus albumin. Red blood count was 5 million. Hemoglobin was 14 Gm. White blood count was 10,000 with 66 per cent lymphocytes.

Laboratory Investigations After Two Days' Treatment with adrenal cortical extract, DOCA, and salt.—Laboratory tests showed: total base 142 meq. per liter; sodium 296.9 mg. per cent; potassium 24.5 mg. per cent; chloride 500.6 mg. per cent; blood urea nitrogen 34.5 mg. per cent; blood sugar 56.6 mg. per cent; cholesterol 219.8 mg. per cent; cholesterol ester 95.2 mg. per cent. Blood culture was negative. X-rays of the chest and abdomen were negative. The tuberculin test was negative.

Laboratory Investigations After Eight Days of Therapy (Feb. 5, 1948).—Laboratory tests showed: total base 140 meq. per liter; blood urea nitrogen 41.4 mg. per cent; sugar 75.2 mg. per cent; sodium 292 mg. per cent; potassium 18.7 mg. per cent; chloride 522.6 mg. per cent.

On Feb. 6, oral saline was stopped but hormone therapy was continued. On the following day the patient developed a respiratory infection. In the next two days he lost 2 pounds and his vomiting and loose stools returned.

Laboratory Investigations at This Time (Feb. 11, 1948).—Laboratory tests showed: total base 141 meq. per liter; sodium 292.1 mg. per cent; potassium 20.0 mg. per cent;

chloride 521.9 mg. per cent; total protein 5.46 Gm. per cent; albumin 2.77 Gm. per cent; globulin 2.69 Gm. per cent. White blood count was 10,800 with 80 per cent lymphocytes. Blood sugar was 65 mg. per cent.

He was again given 300 c.c. of normal saline orally daily and his upper-respiratory infection responded promptly to penicillin. By Feb. 12, 1948, he was again in good condition.

Further Laboratory Investigations Done at This Time.—Laboratory tests showed: glucose tolerance test: fasting 45.2 mg. per cent, one-half hour 113.7 mg. per cent, one hour 134.8 mg. per cent, two and one-half hours 124.5 mg. per cent. Epinephrine tolerance test: fasting 90 mg. per cent, one-half hour 112.4 mg. per cent, one hour 106.3 mg. per cent, one and one-half hours 75.4 mg. per cent. No cystine could be found in the urine. Addis count done at this time was within normal limits. A skin biopsy was done at this time. The 17-ketosteroid excretion was 0.14 mg. per twenty-four hours. Two urine concentration tests showed specific gravity of 1.020 after fluids were withheld for twelve hours. Phenolsulfonephthalein test showed 47 per cent excretion in the first hour and 24 per cent in the second hour; the total was 71 per cent. Intravenous pyelogram was again negative. Examination of the prostate revealed no abnormality.

The patient remained in the hospital until March 3, 1948. About one week before discharge his desoxycorticosterone was discontinued. He continued to take one teaspoonful of salt in his milk each day. During March and April, 1948, the patient had many upper-respiratory infections. He had to be readmitted to the hospital on March 10 and April 8. With each infection the color of his skin became temporarily darker and with improvement it again became golden brown. Quantitative urine examinations were made on both of these occasions, the results of which are discussed later. The patient was again discharged with no treatment other than added salt to the diet.

On April 26, 1948, he was readmitted to the hospital because for the two previous days he had vomited several times and had had several large, green, liquid, foul-smelling stools. He had slept a great deal but could be aroused. Physical examination was not remarkable. White blood count was 15,455 with 48 per cent lymphocytes. Hemoglobin was 10 Gm. Urine analysis at this time showed red blood cells, white blood cells, casts, and a 3-plus albumin. The following day he developed a mild case of measles (he had had immune globulin two weeks before). The patient was started on adrenal cortical extract 1 c.c. intramuscularly every six hours. In forty-eight hours his vomiting and diarrhea had ceased. He had no further difficulty during this admission. The outstanding feature of the admission was the urinary findings listed.

Laboratory Investigations at This Time.—Laboratory tests showed: total base 135 meq. per liter; blood urea nitrogen 15.1 mg. per cent; sugar 66.8 mg. per cent; chlorides (as sodium chloride) 488 mg. per cent; sodium 300 mg. per cent; potassium 24.1 mg. per cent.

The patient was then followed at home on 1 c.c. of Eschatin and added salt in diet (one teaspoonful daily). He did well for a few weeks but again developed an acute tonsillitis on July 9, 1948. He rapidly became listless. Temperature was 103° F. Eschatin was increased to 5 c.c. per day. Parenteral fluids were given. Penicillin was used to treat the primary infection. In a few days he was again doing well. To evaluate the presence of cellular elements which had been noted in the urine from time to time since his attack of measles, an Addis count was done. It was completely normal. Another sodium balance study was done at this time. The patient was again discharged on maintenance doses of 1 teaspoonful of added salt and 1 c.c. of Eschatin intramuscularly daily.

TERMINAL ADMISSION

At 20 months of age on Aug. 12, 1948, the patient was again admitted to the hospital because of fever, listlessness, and irritability when aroused. He did not appear acutely ill and although he seemed to have abdominal pain there were no unusual physical findings. Therapy with penicillin, adrenal cortical extract, and salt produced prompt improvement. However, three days later he again developed fever and diarrhea. He seemed to have severe abdominal pain and respirations were grunting in character. During the next

twenty-four hours he received 100 c.c. per kilogram of body weight of 5 per cent glucose in isotonic saline parenterally, in addition to a liberal intake of sugar solutions by mouth. His mother noted that he was becoming disoriented and did not recognize her. Blood sugar at this time was found to be 33 mg. per cent, and serum sodium chloride 400 mg. per cent. These reports, unfortunately, were not received until the following morning. Urinalysis revealed 2-plus albuminuria and 2.8 Gm. of sodium chloride per liter. Neither sugar nor acetone were found in the urine. Temperature continued to run around 104° F.

At forty-five minutes past midnight on Aug. 18, 1948, the patient suddenly cried out, respirations became grunting and labored, and he had a convulsion lasting several minutes. He was immediately given 20 c.c. of Eschatin and an infusion of normal saline. At 2:30 A.M. the patient had another convulsion. No blood pressure could be obtained. He responded to oxygen but intermittent convulsions continued even under full doses of phenobarbital. A phleboclysis was done and a continuous drip of 5 per cent glucose in saline allowed to run at maximum rate.

Laboratory Investigations at 8 A.M. *on Aug. 18, 1948, With a Continuous Drip of 5 Per Cent Glucose in Saline Running.*—Laboratory tests showed: total base 147.5 meq. per liter; blood sugar 22 mg. per cent; blood urea nitrogen 23 mg. per cent; carbon dioxide 36 volumes per cent; sodium 304.9 mg. per cent; chlorides 578.8 mg. per cent; at 11 A.M. the blood sugar was 62 mg. per cent.

When these results were obtained at 1:30 P.M. the 5 per cent glucose was replaced with 12.5 per cent glucose in saline. When the intravenous drip was running at maximum speed (10 c.c. per kilogram per hour), blood was drawn for complete chemistries. The report was as follows: total base 144.9 meq. per liter; sugar 67 mg. per cent; sodium 304.9 mg. per cent; potassium 19.1 mg. per cent; magnesium 2.2 mg. per cent; calcium 9.7 mg. per cent; chloride 578.9 mg. per cent; phosphorus 5.9 mg. per cent; protein 3.84 Gm.; albumin 1.8 Gm. per cent; globulin 2.04 Gm. per cent; amylase 34.7 units; acid phosphatase 0.06; and alkaline phosphatase 7.0 Bodansky units.

The intravenous drip could not be allowed to run at this rate without flooding the patient so the rate was cut to 4 c.c. per kilogram per hour. Two hours later the blood sugar was 45 mg. per cent. Glucose, a 10 per cent solution, was then given by gavage while 250 c.c. of blood was allowed to drip through the intravenous. At the same time 500 c.c. of one-sixth molar lactate was given subcutaneously. The intravenous administration of glucose in saline was then resumed. One ampule of Solu-B and one of ascorbic acid were added to each 1,000 c.c. of fluid. Eschatin 5 c.c. was given every two hours and 1 c.c. (5 mg.) of Percorten daily. In spite of intensive therapy the patient remained convulsive and in coma until death at 3:30 P.M., Aug. 19, 1948.

The patient received a total of 4,000 c.c. of fluid in the last sixty hours of life (about 140 c.c. per kilogram per day). That even the administration of maximum sodium and glucose containing fluids were of no avail is indicated by the blood chemistries drawn at the time of death. Blood sugar was 30 mg. per cent; total base 117 meq. per liter; sodium 221.3 mg. per cent. Potassium *38.6* mg. per cent. Magnesium 2.8 mg. per cent. Calcium 9.3 mg. per cent; chloride 449.1 mg. per cent; phosphorus 5.0 mg. per cent; protein 3.54 mg. per cent; albumin 1.85 Gm. per cent; globulin 1.69 Gm. per cent.

During the last few hours of life the patient became anuric and edematous.

AUTOPSY FINDINGS

A complete autopsy was performed four hours after death. The body was that of a well-developed, well-nourished, white male infant, 20 months of age, weighing 35 pounds and measuring 34 inches in length. The external genitals were of average size and development with testes in the scrotal sac. There was slight, nonpitting edema of both lower extremities. The skin was soft, pliable, slightly oily, and definitely bronzed. There was no accentuation of this color in the axillary or inguinal region.

There were 90 c.c. of clear, straw-colored fluid in each pleural cavity. The heart and great vessels were not remarkable. The thyroid gland weighed 4 grams and exhibited

a homogeneous, brown glistening surface. The microscopic examination was not remarkable. The thymus weighed 28 grams, the left lobe being approximately twice the size of the right. No unusual changes were noted microscopically.

The lungs were not remarkable. The heart weighed 60 grams. The musculature was dark red, firm, and fibrillar. The valves were normally developed.

The spleen weighed 60 grams. The organ was soft and held its shape poorly and on cut section exhibited a dark red surface with distinct malpighian bodies. Microscopically the red pulp was seen to be moderately engorged with blood.

The liver weighed 690 grams and measured 20 cm. × 12 cm. × 5.5 cm. On cut section the surfaces were chocolate brown in color with indistinct lobular markings. Microscopically the central veins and sinusoids were moderately engorged with blood. The portal triads were not remarkable. A glycogen stain showed no evidence of glycogen.

The pancreas weighed 18 grams and on cut section was pinkish-tan in color and finely lobulated. The pancreatic acini and islands of Langerhans showed no unusual changes.

Adrenals: (Fig. 1.)

Gross: The right adrenal weighed 1.5 grams, the left 1.0 grams. Both adrenals were remarkably small, roughly triangular, the right being flatter than the left. The adrenal vessels were not remarkable. On cut section a fine thin line of dark yellow cortex was seen overlying a grayish-brown central portion. The glands were firm and held their shape well.

Microscopic.—Sections stained with Masson's trichrome showed a capsule of fibrous connective tissue several cell layers thick. A large portion of the area usually occupied by cortex was composed of fibrous connective tissue containing a moderate number of capillaries. With hematoxylin and eosin stain, the zona glomerulosa was seen to be composed of a few scattered groups of cells with eosinophilic cytoplasm and basophilic nuclei, adjacent to capillaries. Extending inward from these cell groups were a few short strands of cells with homogeneous, eosinophilic cytoplasm. In none of these cells was there any evidence of vacuolization. The area usually composed of cells making up the zona reticularis was occupied by vascular connective tissue. Adjacent to the capsule were rounded, well-circumscribed areas of polygonal cells which resembled the fetal reticularis. These cells contained an abundant, homogeneous, pale-staining, eosinophilic cytoplasm and large vesicular nuclei with an occasional eosinophilic nucleolus. The medulla was composed of irregularly shaped, small cells with basilic cytoplasm and small, compact nuclei. Some of these cells seen in the medullary portions resembled those normally seen in the zona reticularis. Amyloid stains were negative.

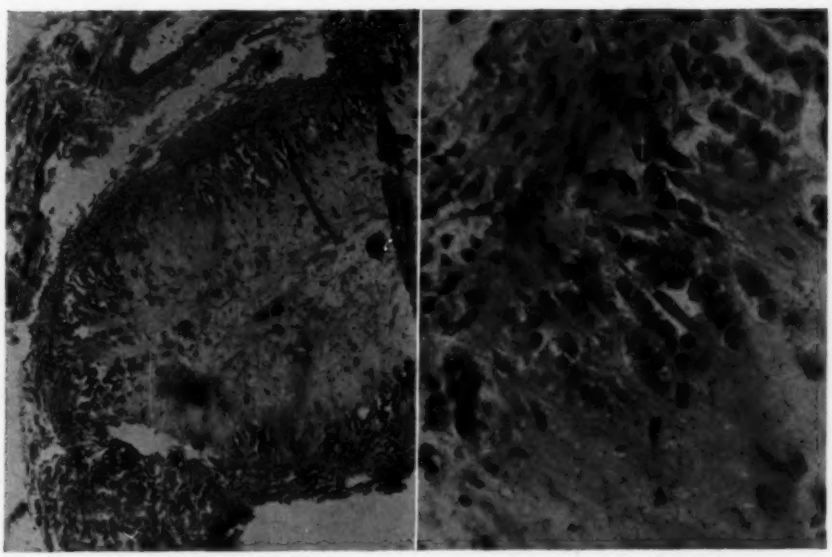
The gastrointestinal tract was not remarkable.

The right kidney weighed 95 grams, the left 90 grams. Fetal lobular markings were present. On cut section, the surfaces bulged slightly. The kidney substance was of average thickness with a well-defined corticomedullary junction. The pelves and ureters were thin walled. The urinary bladder was not remarkable. The prostate was small, symmetrical, and homogeneous in appearance. The testes on cut section showed a pale, tawny surface with small, filamentous tubules. The cells of the seminiferous tubules showed mitotic activity but no spermatogenesis. Scattered interstitial cells of Leydig were present.

The cells of the basal layer of the epidermis contained a light brown, granular, nonrefractile pigment which did not take an iron stain.

The brain weighed 1,230 grams. There was a moderate increase in subarachnoid fluid. The leptomeninges were thin and transparent. The gyri appeared slightly flattened and the sulci widened. Microscopically the cortex showed the usual stratification but no loss of cellular polarity. Neuronophagia was not seen and cellular detail was well preserved. The perivascular clear spaces were large, vacuolization was prominent, and the white matter of the cortex presented a loose, edematous appearance. A few small, focal perivascular hemorrhages were present in the medulla near the floor of the fourth ventricle.

A.



B. *C.*

Fig. 1. (Case D. S.)—*A*, gross appearance of the adrenals and kidneys. *B*, Microscopic section of the adrenal gland. (Hematoxylin and eosin ×105.) *C*, Microscopic section of the adrenal gland. (Hematoxylin and eosin ×475.)

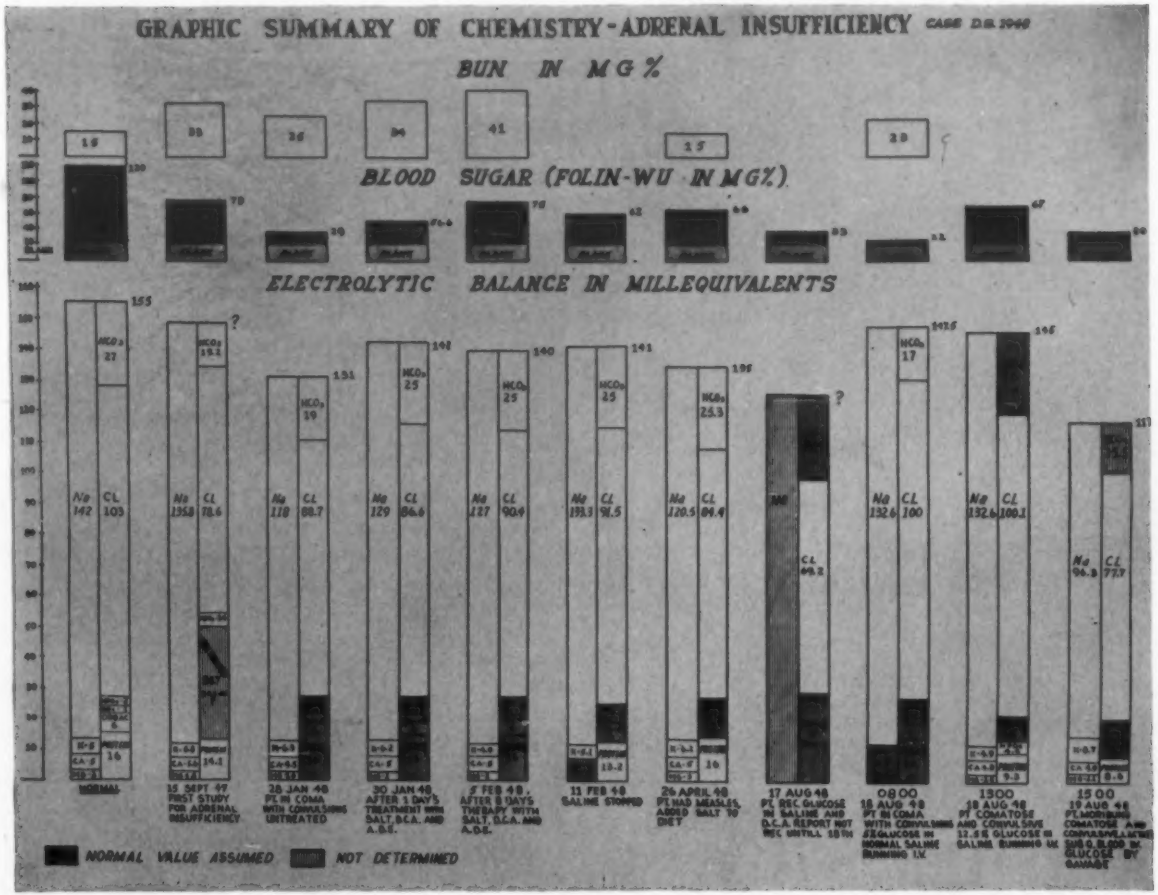

GRAPHIC SUMMARY OF CHEMISTRY - ADRENAL INSUFFICIENCY CASE D.S. 2960
BUN IN MG %
BLOOD SUGAR (FOLIN-WU IN MG%)
ELECTROLYTIC BALANCE IN MILLEQUIVALENTS
NORMAL
15 SEPT 47 FIRST STUDY FOR ADRENAL INSUFFICIENCY
28 JAN 48 PT IN COMA WITH CONVULSIONS UNTREATED
30 JAN 48 AFTER 1 DAYS TREATMENT WITH SALT, D.C.A. AND A.D.S.
5 FEB 48, AFTER 8 DAYS THERAPY WITH SALT, D.C.A. AND A.D.S.
11 FEB 48 SALINE STOPPED
26 APRIL 48 PT HAD MEASLES, ADDED SALT TO DIET
17 AUG 48 PT. REC. GLUCOSE IN SALINE AND D.C.A. REPORT NOT REC. UNTIL 18 TH
0800 18 AUG 48 PT IN COMA WITH CONVULSIONS 12.5% GLUCOSE IN NORMAL SALINE RUNNING I.V.
1300 18 AUG 48 PT COMATOSE AND CONVULSIVE 12.5% GLUCOSE IN SALINE RUNNING I.V.
1500 19 AUG 48 PT. MORIBUND COMATOSE AND CONVULSIVE NO BLOOD IN GLUCOSE BY GAVAGE
NORMAL VALUE ASSUMED
NOT DETERMINED

Chart I. (Case D. S.)—Chemistry in case of adrenal insufficiency. Methods used for chemical determinations are as follows: *Blood*: total base, method of Fiske and Sunderman; sodium, method of Weinbach; potassium, method of Breh and Gaebler; chloride, method of Schales and Schales; sugar, method of Folin; protein, method of Greenberg. *Urine*: 17-ketosteroids, method of Pincus.

In the *pituitary*, the acidophilic-type cells of the pars distalis showed an abundant, pink cytoplasm and were much more numerous than the basophilic type. The basophilic type cells showed little cytoplasm, no granules, and were difficult to define.

Sections of lymph nodes showed a connective tissue framework consisting of a capsule and trabeculations. Lymphatic nodules were numerous, small, and exhibited central germinal centers, surrounded by a thin zone of lymphocytes. An occasional eosinophilic leucocyte was seen.

Comment.—In this case, as in cases of primary adrenal atrophy, the connective tissue stroma appeared collapsed, and not increased in amount. Vascularization was prominent. No lymphocytes were seen in the stroma in this case. In primary atrophy the stroma is infiltrated with lymphocytes and the cortical cells are likely to be large and exhibit bizarre nuclei. In this case the cortical cells were regular in size and shape. No evidence of tuberculosis or amyloid disease was noted. The stroma consisted of areolar connective tissue rather than dense fibrosis of the type which would be expected as the end result of hemorrhage. Normally as fetal cortex disappears, it is replaced by true cortex and medulla. In this case the medulla apparently developed normally, but following neonatal involution of the fetal cortex the adult cortex failed to develop normally. We have interpreted this as representing congenital adrenocortical hypoplasia. This case is so coded by the Armed Forces Institute of Pathology.

It has been suggested[4] that the zona glomerulosa is the source of the salt and water factor, the fasciculata is the origin of the "S" factor, and the reticularis the producer of the "N" factor. The adrenal morphology in this case supports this hypothesis. The patient exhibited primarily a disturbance of carbohydrate metabolism, and only a trace of the zona fasciculata could be found. The zona glomerulosa was diminished, but present, and the patient exhibited a relative stability of salt and water balance. Normal growth and positive nitrogen balance exhibited by this patient indicated the presence of some "N" factor. Since the zona reticularis was not evident, it may be assumed that the "N" factor was elaborated by the multiple rests of fetal cortex noted beneath the capsule.

SUMMARY OF PERTINENT POINTS WITH DISCUSSION OF THE CASE

Consideration of the known functions of the adrenal cortex is essential for the interpretation of symptoms, signs, and the results of laboratory investigations in any case suspected of having aberrant adrenal function. A recapitulation of the better-established functions is as follows: (1) The retention of sodium and water, and the elimination of potassium, by the kidney. This function is controlled by hormones related to 11-desoxycorticosterone which have been called "salt and water hormone(s)". (2) Hormone(s) which promote catabolism (gluconeogenesis) are related to 11-dehydro-17-hydroxycorticosterone. Albright[5] proposed the term "S" hormone for this group of steroids since they are concerned with sugar metabolism. (3) Anabolic activity and nitrogen retention is favored by the action of a group of steroids related to the androgens (estrins and progestin are also produced by the adrenal). Because of their effect on nitrogen balance Albright[5] proposed the term "N" hormone(s) for this group, and suggested that they were antagonistic to the "S" hormone(s).

1. Disturbances of Salt and Water Metabolism: Case D. S. Blood electrolyte values in millequivalents are summarized in Chart I.* When this patient was 9 months old (Sept. 15, 1947), investigation of blood chemistry for evidences of Addison's disease was conducted. Although the blood chloride was very low,

*These chemical determinations were provided by D. M. Goss, Addelia Peterson, and Jane Neff of the Fourth Army Laboratory, Brooke Army Medical Center, Fort Sam Houston, Texas, Col. D. M. Kuhns, Commanding Officer.

Blood: total base, method of Fiske and Sunderman; sodium, method of Weinbach; potassium, method of Breh and Gaebler; chloride, method of Schales and Schales; sugar, method of Folin; protein, method of Greenberg. *Urine*: 17-ketosteroids, method of Pincus.

values for sodium and potassium were within normal limits. Unfortunately, total base was not determined on Sept. 15, as it would have served as a check. Subsequent experiments with various standard sodium solutions showed that the method used gave values too high. This was believed to be due to the saturated acetone wash reagent. For the remainder of the determinations the method used was that of the Army Medical School.

As can be seen from the chart this patient demonstrated the low sodium and high potassium characteristic of adrenal insufficiency. In general, however, he maintained his internal equilibrium fairly well. It was only during periods of stress that disturbances of blood electrolytes were present. The grossly abnormal values terminally probably resulted from collapse of the barrier between intra- and extracellular spaces since the patient was anuric.

TABLE I. SODIUM, POTASSIUM, AND NITROGEN BALANCE STUDIES

STABILIZED ON DAILY INTAKE PRIOR TO AND DURING COLLECTION PERIOD	MARCH 15, 1948 48-HR. PERIOD TEASPOONFUL SALT/DAY NO HORMONES	APRIL 16, 1948 24-HR. PERIOD DESOXYCORTICOSTERONE 3 MG. NO SALT ADDED	APRIL 19, 1948 24-HR. PERIOD NO DESOXYCORTICOSTERONE OR SALT ADDED	JULY 14, 1948 24-HR. PERIOD TEASPOONFUL SALT-DAY NO HORMONES
Intake				
Milk (c.c.)	3,200	1,280	1,152	1,200
Sodium (mg.)	4,400	490	490	2,100
Potassium (mg.)	4,928	1,971	1,774	1,848
Nitrogen (mg.)	7,700	2,716	2,534	2,640
Output				
Volume (c.c.)	2,000	780	670	825
Sodium (mg.)	5,200	520	560	740
Potassium (mg.)	2,730	1,700	1,910	899
Chloride as NaCl (mg.)	14,000	2,500	2,000	3,480
Total nitrogen (mg.)	8,600			5,000
Urea (mg.)	11,400			5,500
Uric acid (mg.)	460			151
Creatinine (mg.)	3.6			1.0
Albumin (mg.)	1,500	700	737	1,110
Sugar	Neg.	Neg.	Neg.	Neg.
Coproporphyrins	247 gamma	43 gamma	70 gamma	112 gamma
Uroporphyrins	Neg.	Neg.	Neg.	Neg.
Addis count	Normal	Normal	Normal	Normal
Balances				
Sodium in mg.	-800	-30	-70	+1,360
Potassium in mg.	+2,198	+271	-144	+949
Nitrogen in mg.	-900			-2,360

Balance studies were run on this patient on four different occasions. Quantitative analysis of urine specimens collected over a twenty-four hour or forty-hour period are reported in Table I. We realized that these periods were too short to be indicative of the situation, but we were unable to continue them because the patient always developed edema and inflammation of the penis after even these short collection periods. Each of these specimens were collected after the patient had recovered from a respiratory infection, was in good condition, and had been stabilized on therapy as indicated. Our first three studies were evidently conducted during recovery from acute illnesses when the patient had not yet begun to store sodium, and was retaining potassium. On the last study he was evidently further along on the road to homeostasis.

2. Disturbances of Carbohydrate Metabolism: Chart II demonstrates alterations of carbohydrate metabolism in this patient that are characteristic of adrenal insufficiency.[6] Since these blood sugars were run by the method of Folin and Wu the blank is indicated on the charts. The oral glucose tolerance test produced a flat curve. The intravenous glucose tolerance test resulted in some elevation of blood sugar. An insulin tolerance test produced hypoglycemia and preconvulsive movements before it was terminated. Epinephrine produced a fairly normal elevation of blood sugar, but if it had been repeated immediately,

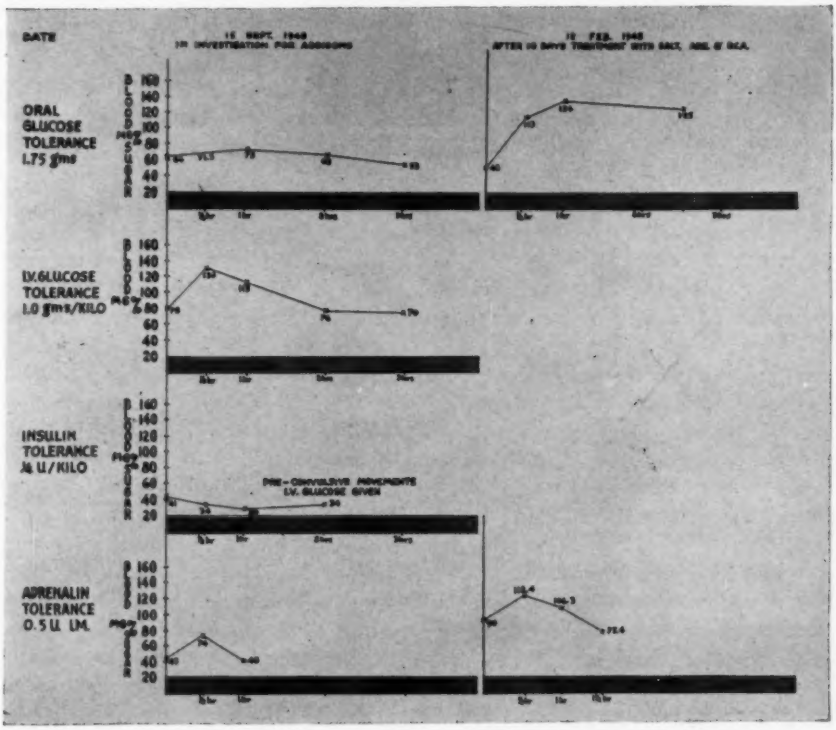

DATE
ORAL GLUCOSE TOLERANCE 1.75 gms
I.V. GLUCOSE TOLERANCE 1.0 gms/KILO
INSULIN TOLERANCE .4 U/KILO
ADRENALIN TOLERANCE 0.5 U. I.M.

Chart II.—Carbohydrate metabolism in case of adrenal insufficiency in infancy. Case D. S., 1948.

the response would, no doubt, have been less complete. Blood specimens taken at random are also typical in that the patient maintained blood sugar levels of low normal but immediately developed hypoglycemic levels during periods of stress. (Chart I.) This patient seemed to do well as long as his carbohydrate intake was adequate. Evidently he produced insignificant amounts of the "sugar factor" and gluconeogenesis was inhibited. During his terminal crises it was impossible to maintain normal levels of blood sugar with 10 per cent glucose intravenously. He was evidently unable to form glucose from his own body protein and fat (although he was well nourished). After the patient

developed a constant convulsive state it was impossible to administer, parenterally, enough glucose to avoid hypoglycemia. The administration of alloxan was considered, but the notion discarded, because it produces hypoglycemia before hyperglycemia. The complete exhaustion of glycogen reserves is indicated by the following analyses of specimens carefully collected directly into a solution of potassium hydroxide three hours after death.

Organ	*Glycogen Content*	*Normal Values*
Liver	0.097 mg. per cent	0.2 to 10 mg. per cent
	0.037 mg. per cent	
Rectus muscle	0.004 mg. per cent	0.2 to 1.8 mg. per cent
Diaphragm	0.007 mg. per cent	

The cortical extract administered during this interval (Eschatin—60 c.c. per twenty-four hours) seemed insufficient to elevate blood sugar, decrease the peripheral utilization of glucose, or promote glycogen storage in either liver or muscle.

3. Pigmentation: Of the cases of adrenal insufficiency in infancy, four of the well-documented cases were reported to have pigmentation characteristic of Addison's disease. No patient had definite pigmentation of the mucous membranes. These descriptions apply to our patient. Pigmentation was not more extreme than that noted in many normal children. It resembled a good sun tan. There was no pigmentation of the mucous membranes. The most notable feature was the marked increase in pigmentation during periods of stress or dehydration. It then became almost black over the backs of the hands, genitals, areolae, and on the extensor aspects of the feet. This pigmentation was demonstrated to be due to melanin by study of skin specimens by biopsy.

4. Disturbances of Growth: At this hospital it is routine practice to follow all infants on the Wetzel Baby Grid. Attention was first directed to this patient because of a type of growth failure on the grid which we have come to associate with congenital anomalies. It has been described by Wetzel[7] and consists of an auxodrome lag not accompanied by the low angle drift characteristic of simple malnutrition. The delay in speed of development is indicated by the achievement of only level 85 at age 6 months when he should have reached level 65 (Fig. 2). On repeated radiologic surveys bone age was compatible with chronological age.

The marked acceleration of growth which this patient demonstrated during periods in which he was not subject to stress (as between 10 and 11 months of age) might be predicted in a patient lacking in the "S" factor. The "S" factor, being catabolic, produces dwarfism when given to growing animals.[6] The opposite would naturally be expected in this patient since deficiency of the "S" factor was demonstrated. The small amount of androgen or "N" factor being anabolic and *unopposed* would result in increased somatic growth. The embryonic androgenic tissue noted in the capsule of the adrenal probably produced the androgens.

5. Blood Pressure: In this case the blood pressure was always normal except during periods of stress when hypotension became evident and the diastolic pressure often not obtainable.

6. Gastrointestinal Disturbances: Although anorexia is noted in most cases of Addison's disease in adults, it was never marked in this case. It is noteworthy that, especially during early infancy, vomiting was severe, but that diarrhea was never a serious problem. No salt craving was ever apparent.

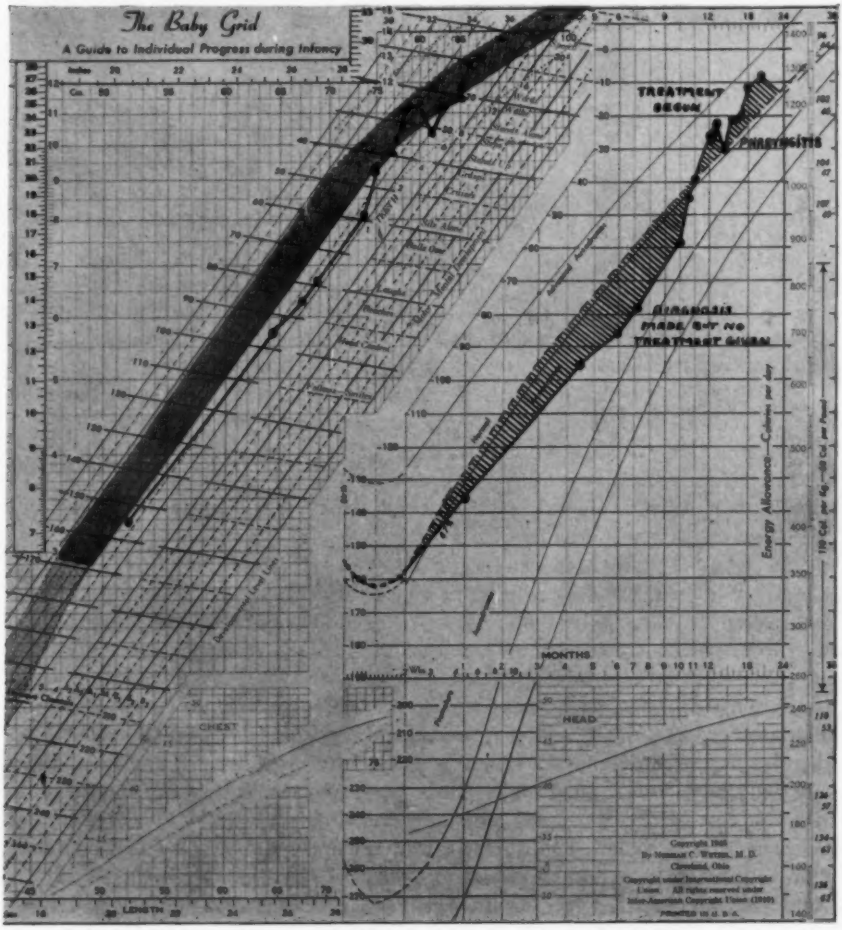


Fig. 2. (Case D. S.)—Growth and development of patient with adrenal insufficiency.

Repeated x-ray examination of the gastrointestinal tract revealed no evidence of abnormality. This patient had severe abdominal pain early in his crises. The abdominal pain seemed more closely related to blood sugar level than to low blood sodium.

7. Asthenia: Our patient never exhibited asthenia despite demonstrated deficiency of the "S" factor. This is rather surprising in view of the fact that

one method of biologic assay of the potency of 11-hydroxycorticosteroids is their ability to support the work capacity of muscle.

8. Excretion of 17-Ketosteroids. Twenty-four hour specimens of urine were examined for 17 ketosteroids by the method of Pincus on six different occasions. The average excretion level was 0.12 mg. per twenty-four hours, as androsterone.

9. Unfortunately no investigations of the basal metabolic rate or electrocardiography were conducted on this patient. Repeated chest films were done and no evidence of microcardia was detectable.

10. Blood counts were done on at least fifty occasions. The red blood count averaged 4,200,000 and hemoglobin 12 Gm. The white blood count averaged 10,100 with 56 per cent lymphocytes. During periods of stress the relative lymphocytosis expected occurred. During his first admission in coma and during his terminal illness, over 80 per cent of the circulating white blood cells were lymphocytes. Evidently the normal dissolution of the lymphocytes during periods of stress failed to occur.

11. Urologic Examination: This patient had repeatedly normal intravenous pyelograms. Studies both in vivo and in vitro showed no evidence of pseudohermaphroditism.

12. Crises: The failure of the normal resistance to nonspecific and specific stress is indicated by the clinical course of this patient since episodes of minor nature, which the normal infant tolerates easily, resulted in the collapse of the patient. Our laboratory studies corroborate the observations of Soffer[6] in that crises occurred with normal electrolyte patterns. The failure of the normal "S" hormone response was predominant.

13. Renal Function in Addison's Disease: In the differential diagnosis of adrenal insufficiency in infancy, congenital anomalies of the kidney cause the most confusion. This is especially true of individuals with tubular nephropathy, who demonstrate relative inability to reabsorb sodium. Such cases are not foreign to the experience of any large pediatric center.[8] We have studied several such patients. Somewhat similar clinical entities, on an acquired basis, have been reported by Thorn.[9] In our case of adrenal insufficiency, some doubt was cast upon the diagnosis, because of the discovery of formed elements, casts, and albumin, in random urine specimens. Quantitative examinations repeatedly showed less than 1 Gm. of albumin excretion in twenty-four hours and normal Addis counts. Our patient also had a rather persistent elevation of blood urea nitrogen although the usual tests of kidney function and nitrogen balance studies were within normal limits. It is worthy of note that nitrogen retention was less marked during periods of crises when gluconeogenesis was inhibited.

14. Treatment: Our patient evidently had primarily a deficiency of the "S" factor, not previously reported in infancy. This is as might be suspected from a study of the microscopic sections of the adrenal. In most of the reported cases of adrenal insufficiency in infancy there has been a persistence of the "fetal" cortex interfering with the zona glomerulosa. The zona fasciculata has been well preserved.[10] In our case the zona glomerulosa, although not normal, was better preserved than the remainder of the cortex. If the human adrenal

cortex functions like that of the rat, this picture would be expected to result primarily in the failure of gluconeogenesis, and not in deficiency of the salt and water factor.[10]

During the life of this patient, clinical study indicated that whole adrenal-cortical extract should be more effective than desoxycorticosterone. The failure of the whole adrenal extract available for the treatment of this patient is explained by the following observations from Cameron.[11] It requires the extract of 2,000 Gm. of beef adrenal cortex to bring an adrenalectomized cat out of crisis. One cubic centimeter of commercial adrenal extract is equivalent to 100 Gm. of beef adrenal. More adrenocorticosteroid activity can be demonstrated in the blood flowing from the adrenal vein of a 10-kilogram dog in twenty-four hours than can be isolated from 17 Kg. of fresh beef adrenals.

Therefore, the 60 dollars worth of whole adrenal extract (60 c.c.) which this patient received in twenty-four hours during his terminal crisis, is only the equivalent of 6,000 Gm. of beef adrenal. This is approximately one-third the amount theoretically required. It probably would not have been sufficient for an adrenalectomized cat whose glycogen stores were as exhausted as those of this patient.

REVIEW

A case report such as this has little significance without some orientation regarding its relationship to previously reported cases. The following clinical classification and summary of reported cases is offered for orientation, and as an aid in the evaluation of cases of adrenal insufficiency encountered in infancy. It is constructed from the firm basis of the cases of adrenal insufficiency occurring in infancy which have been reported.

Clinical Classification of Adrenal Insufficiency in Infancy

I. "Pure Adrenal Insufficiency" or "Addison's Disease."—

This group includes those cases in which there is a decrease in all the known functions of the adrenal cortex. The salt and water factor, the "S" factor, and the "N" factor are independently variable. The absence of one of these functions may be more apparent than the others, but all are decreased, and none are increased.

A. Aplasia of the adrenal cortex: Aplasia is found frequently in association with other congenital anomalies, especially anencephalia, but is probably incompatible with life.

B. Hypoplasia of the adrenal cortex: In any textbook of pathology a discussion of the clinicopathologic effects of hypoplasia of an organ usually follows the discussion of aplasia. The only reported case of hypoplasia of the adrenal cortex is the case described in detail in this paper.

C. Hypofunction of the adrenal cortex during early life: A survey of the literature indicates that embryologists, histologists, and pathologists have long been aware of the possible implications of the striking differences between the adrenal glands of the fetus and those of the adult. Blackman[12] has shown that the "fetal," "reticular," or "androgenic" zone atrophies rapidly at term and that the few cells which persist develop into the adult reticular zone. Astute

clinical observers have wondered about the possible clinical importance of these changes. Since relatively potent extracts of the adrenal gland have been available, empirical clinical observations have suggested that such extracts are of value under a variety of circumstances.[13, 14, 15, 16, 17] In the American literature the most prominent exponent of the concept that temporary hypoadrenia may occur during this transition period has been Jaudon.[18] Some 5,000 infants delivered at this hospital during the three years following Jaudon's first report have been closely watched for evidence of this syndrome. In our experience about 1 in 1,000 newborn infants demonstrate evidence of adrenal insufficiency sufficient to warrant the empirical administration of cortical extracts and the addition of salt to the diet. With such therapy our patients have survived, so there has been no opportunity for post-mortem investigation of the adrenals. In two premature infants such therapy has, however, seemed of vital importance for several months.

The case herein reported, of proved adrenal insufficiency, provides a standard for the study and evaluation of such cases as may be encountered in the future.

D. Adrenal insufficiency due to destruction of the adrenal cortex:

1. Acute Adrenal Insufficiency.—Sudden destruction of the adrenal cortex or exhaustion of the adreno-cortical reserve produces a picture of "medical shock."

(a) Adrenal hemorrhage in the newborn: The clinical syndrome exhibited by these patients has been delineated by the papers of Goldzieher and Gordon.[19] Over 100 such cases have been reported but few are supported by premortem clinical studies. We have seen only one such case in the last 10,000 newborn infants delivered at this institution. Some patients probably survive[19] and may later show signs of Addison's disease.

(b) Adrenal hemorrhage in older infants: The Waterhouse[20] and Friderichsen[21] syndrome. Recently reports of survival have begun to appear.[22] Whether the adrenals were actually involved in the cases of patients who survived cannot be determined. Although meningococcemia is responsible for more than 60 per cent of such cases,[23] other organisms may produce the same phenomena.[24] Necrosis of the adrenals during the course of other acute infections and toxemias has been reported.[25] Whether the hemorrhage into the cortex is primary or secondary to exhaustion of adrenal cortical reserve is unknown.[26] Selective adrenal necrosis from chemicals also occurs.[6] The same group of symptoms have been seen in patients who, at autopsy, had only meningococcic septicemia without adrenal hemorrhage.[27] A recent paper on this subject in pediatric literature is that of Ceballos[22] who states that more than 100 such cases have been reported. Over 90 per cent of the patients have been under the age of 2 years. More complete laboratory examinations may substantiate the presence of adrenal insufficiency in future cases. Patients who recover should be followed for signs of the development of latent Addison's disease.[27]

2. Chronic Adrenal Insufficiency.—Progressive destruction of the adrenal glands produces the clinical picture of classical Addison's disease. Although

tuberculosis of the adrenal glands has been the most common cause of Addison's disease in the past, atrophy of the adrenal glands of unknown origin now seems to be more common.[6] The only case of chronic hypoadrenia due to destruction of the adrenal glands in an infant actually reported is that of Jaudon.[3]

II. Hypoadrenia Associated With Anomalies of the Urogenital Tract of Prenatal Origin.—

A. Male pseudohermaphroditism (embryonic hypoplasia of the fetal androgenic zone): It has been postulated that the prominent fetal androgenic zone functions as a sex organ in utero producing androgen to counteract the flood of maternal estrogens (from the ninth to the seventeenth week) before the acidophilic cells of the pituitary appear and begin to function.[28] If this is true, it follows that failure of this defense in male infants would favor a female type of differentiation of the genital ridge since maternal estrogens would be in preponderance. Pseudohermaphroditism is seven times more common in male than in female infants.[29] Such infants might show associated hypoadrenia since the factors which result in failure of embryonic differentiation of the androgenic zone might also interfere with the development of the true cortex. To our knowledge the only case of male pseudohermaphroditism in which hypoadrenia has been demonstrated is the case reported by Jaudon previously referred to.[3] In this patient hypoadrenia was demonstrated during life. The final pathologic diagnoses[30] were: partial aplasia of the adrenals; hyperplasia of the thymus; aplasia of the female sex organs (only 1 cm. of vaginal sac and normal clitoris present); undescended left testicle; lymphatic hyperplasia of the spleen; fatty infiltration of the liver and heart; dilatation of the right ventricle; hypertrophy of the heart.

B. Female pseudohermaphroditism (embryonic hyperplasia of the fetal androgenic zone: Hyperplasia of the embryonic adrenal cortex (with excess androgen production?) in the female fetus results in male differentiation of the genital ridge. That female pseudohermaphroditism is associated with congenital hyperplasia of the adrenal cortex was established by Marchand[31] and confirmed by Glynn.[32] Wilkins,[33] in 1948, found no proved case of other etiology. Female pseudohermaphroditism is actually relatively common since Young[34] estimated the incidence of pseudohermaphroditism at 1 in 1,000 individuals. Bartrud and Thompson[35] found only eighty-three proved cases of female pseudohermaphroditism under the age of 10 years reported. Only six were known to have associated adrenal insufficiency. Allibone[36] reported five additional cases of female pseudohermaphroditism due to bilateral adrenal hypertrophy which were associated with hypoadrenia. These cases were collected from the records of the last ten years from one hospital. Ages at death were 17, 25, 35, 44, and 82 days.

An additional case was recently reported by Chenoweth.[37] Zuelzer[10] reported three cases and found an incidence of 0.52 per cent in autopsies done on infants under 1 year of age. A familial pattern is apparent in many of these cases.[10, 36, 38] Pantos[39] discovered two such cases during an interval of less than six months. In his cases pseudohermaphroditism was established by

urologic examination, demonstration by the injection of radiopaque material into the urogenital sinus, and by operative exploration. Hypoadrenia was demonstrated in these patients during life by thorough laboratory investigation. A total of seventeen cases of adrenocortical insufficiency associated with female pseudohermaphroditism have therefore been reported.[40] Anatomic and histologic examination of the adrenals in all these cases showed diffuse hyperplasia of the androgenic zone with apparent replacement of the zona glomerulosa by eosinophilic cells containing fuchsinophil granules.[10] The physiologic disturbance appears to be one of overproduction with respect to "N" hormone and underproduction of substances regulating salt and water metabolism. The carbohydrate metabolism is apparently intact. This is in marked contrast to the case of hypoplasia reported in this paper. The mechanism concerned in the Addisonian-like symptoms occurring in congenital adrenal hyperplasia have recently been discussed by Wilkins and Lewis.[41] It seems reasonable to believe that in the future reports of well-documented cases of female pseudohermaphroditism associated with hypoadrenia will be more common. Patients with hypospadius should always be suspected of pseudohermaphroditism and appropriate investigation carried out.

C. Embryonic hypoplasia of the fetal androgenic zone in the female fetus or embryonic hyperplasia of the fetal androgenic zone in the male fetus would be expected to result only in some isosexual pseudoprecocity. When hyperplasia of the androgenic zone persists beyond fetal life, macrogenitosomia praecox results. This is discussed in the following section.

III. Hypoadrenia Associated With Postnatal Development of the Adrenogenital Syndrome.—

The salt and water factor, the "S" factor, and the "N" factor being independently variable, cases occur in which one factor is increased and the others are normal or decreased. An excess of the "N" factor in postnatal life produces the adrenogenital syndrome.

A. Adrenal insufficiency associated with macrogenitosomia praecox: Butler,[42] Wilkins,[43] Thelander,[44] and Darrow[45] almost simultaneously reported carefully studied cases of adrenal insufficiency associated with macrogenitosomia. The patient described by Butler, recognized and treated early in infancy, is still alive at 11 years of age and shows persistence of his water and electrolyte disturbance, deep pigmentation, extreme virilism, and dwarfing. An additional case was recently reported at a conference at the New York Hospital.[46] Symptoms of adrenocortical insufficiency occur in these patients before macrogenitosomia becomes evident. A deficit of the salt and water factor seems to be the primary disturbance in the metabolism of these patients. In the cases studied to date, carbohydrate metabolism has been relatively intact. Overproduction of "N" hormone is indicated by the excretion of excess amounts of 17-ketosteroids in the urine, although virilization and macrogenitosomia may not be evident during the first few months or years of life. Hyperplasia of the fetal androgenic zone of the adrenal cortex was discovered at operation or autopsy in these patients. The clinical history frequently reveals the death of a sibling pseudohermaphrodite of adrenal insufficiency.[42, 44]

The literature also contains reports of cases of adrenocortical insufficiency in male infants secondary to hyperplasia of the embryonic cortex but without any obvious manifestations of androgenic components.[10, 36, 47, 48] These patients died after a short, stormy, neonatal course, characterized by inability to gain weight, progressive dehydration, severe episodes of vomiting, and/or diarrhea and sudden collapse. Except for the five cases previously mentioned, there has been insufficient investigation ante mortem to establish definite evidence of adrenocortical insufficiency. Allibone,[36] however, noted the persistence of urinary chloride in two of his cases and suggests that "in cases of obscure intractable vomiting, if the chlorides do not virtually disappear from the urine, adrenal cortical hypofunction should be considered to be a possibility." It should be noted that although hyperadrenia has been reported more often in the female, the number of cases associated with hypoadrenia of one of adrenal corticoids is almost the same in the two sexes. It seems possible that the symptom complex produced by hyperplaia of the adrenal in the female is more dramatic than that in the male and thus more easily recognizable. The different ratio between the sexes is probably more apparent than real. Allibone[36] states that "the equal distribution between the sexes, together with the comparatively frequent reports of familial occurrence, suggests that there is an inherited factor determining the hyperplasia of the suprarenals and that this factor is not sex linked."

B. Postoperative adrenal insufficiency following the removal of a functioning adrenal tumor: In the remainder of the cases of adrenogenital syndrome reported, macrogenitosomia in males or virilization in females has been produced by functioning tumors of the adrenal. Wilkins[40] collected forty-one such case reports, but none were associated with adrenal insufficiency. By definition Cushing's disease consists of a symptom complex due to hyperadrenocorticism with imbalance of all three types of adrenocortical hormones at a high level. No evidence of hypoadrenia was noted in the twenty-six cases reported.[40] Hyperfunction of an adrenal tumor usually results in suppression of the contralateral gland.[49] The operative removal of such a tumor often produces very severe adrenal insufficiency.

IV. Functional or Relative Adrenal Insufficiency.—

Only the introduction to the most fascinating chapter on adrenal cortical insufficiency has yet been written. As the previous discussion has indicated, the incidence of proved cases of adrenal insufficiency is very low. There is much circumstantial evidence available to support the hypotheses that although proved cases of adrenal insufficiency are rare, functional adrenal insufficiency may be a common clinical problem.[5, 26] Future clinical and experimental investigation may provide a more firm foundation for the brilliant theories advanced. Although these premises have not yet been firmly established they are compatible with the facts as we now know them. As ACTH and cortisone become available their validity can be evaluated more exactly. It seems possible that *in the future,* various diseases in which clinical observation has indicated some element of adrenal failure, and perhaps others, may require selective therapy with various corticosteroids not now available.

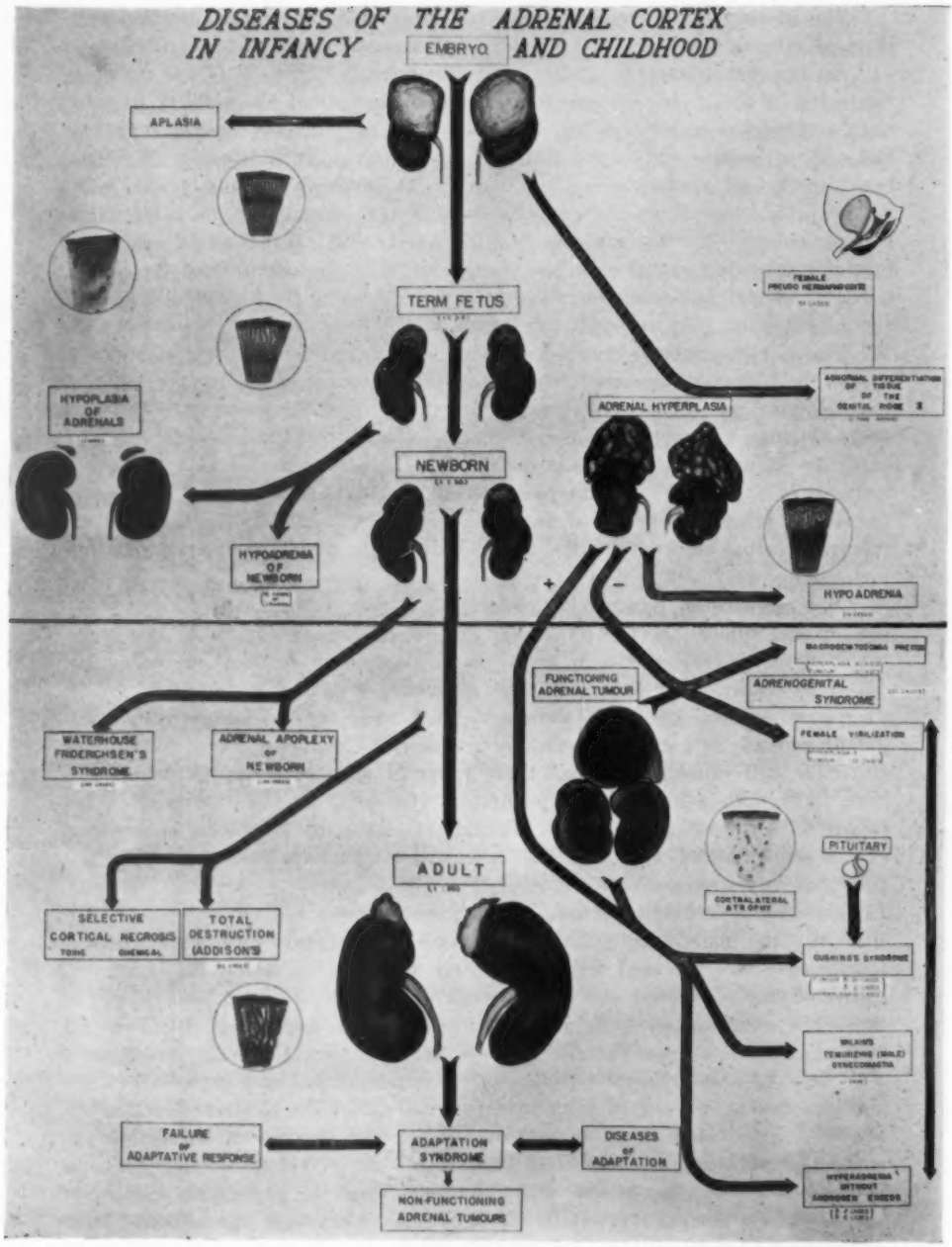

DISEASES OF THE ADRENAL CORTEX IN INFANCY AND CHILDHOOD
EMBRYO
APLASIA
TERM FETUS
NEWBORN
ADULT
HYPOPLASIA OF ADRENALS
HYPOADRENIA OF NEWBORN
ADRENAL HYPERPLASIA
HYPOADRENIA
FUNCTIONING ADRENAL TUMOUR
ADRENOGENITAL SYNDROME
FEMALE VIRILIZATION
WATERHOUSE FRIDERICHSEN'S SYNDROME
ADRENAL APOPLEXY OF NEWBORN
SELECTIVE CORTICAL NECROSIS
TOTAL DESTRUCTION (ADDISON'S)
CONTRALATERAL ATROPHY
PITUITARY
CUSHING'S SYNDROME
FAILURE OF ADAPTATIVE RESPONSE
ADAPTATION SYNDROME
DISEASES OF ADAPTATION
NON-FUNCTIONING ADRENAL TUMOURS

Fig. 3.

CONCLUSIONS AND SUMMARY

1. Figure 3 is a schematic chart constructed from reported cases. It summarizes the interrelationship of the diseases of the adrenal cortex in infancy and childhood and provides a graphic concept of the clinical classification of adrenal cortical insufficiency as presented in this paper.

2. Clinical and laboratory studies conducted ante and post mortem on an infant who had adrenal insufficiency because of hypoplasia of the adrenal glands bilaterally, revealed the characteristic changes of the electrolyte patterns, abnormal carbohydrate metabolism, and low ketosteroid excretion. Clinically this patient exhibited vomiting, diarrhea, increased pigmentation of the skin, disturbances of growth, hydrolability and "crises" with the usual febrile illnesses. Terminally he developed irreversible hypoglycemia. This was correlated with examinations conducted at autopsy which revealed complete absence of glycogen in the liver and striated muscle. Substitution therapy with available whole adrenal preparations was only partially effective.

3. This is believed to be the first case of adrenal insufficiency reported in infancy not associated with intersexuality, the first case to show primarily disturbance of carbohydrate metabolism, and the first in which normal resolution of the embryonic cortex occurred but subsequent development of the true cortex was incomplete (hypoplasia of the adrenal cortex).

Since this paper was written two additional cases of adrenal insufficiency in infancy have been reported in the literature.[50, 51] They represent examples of the types of pathologic entities responsible for the clinical syndrome of hypofunction of the adrenals in early life described by Jaudon.[18]

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REFERENCES

1. Addison, T.: On Disease of the Suprarenal Capsules, London Med. Gaz. 43: 517, 1849.
2. Jaudon, J. C.: Addison's Disease in Children, J. PEDIAT. 28: 733, 1946.
3. Jaudon, J. C.: Addison's Disease in an Infant, J. Clin. Endocrinol. 6: 558, 1946.
4. Talbot, M. B.: Panel Discussion: Physiology of Adrenal Cortex, Pediatrics 3: 519, 1949.
5. Albright, F.: Cushing's Syndrome, The Harvey Lectures 38: 123, 1942-1943.
6. Soffer, L. J.: Diseases of the Adrenals, Philadelphia, 1946, Lea & Febiger.
7. Wetzel, N. C.: The Treatment of Growth Failure, Pediatric Progress, Philadelphia, 1948, F. A. Davis Company.
8. Williams, R. H., and Henry, C.: Nephrogenic Diabetes Insipidus Transmitted by Females Appearing During Infancy in Males, Ann. Int. Med. 27: 84, 1947.
9. Thorn, G. W., Koepf, G. F., and Clinton, M.: Renal Failure Simulating Adrenocortical Insufficiency, New England J. Med. 231: 76, 1944.
10. Zuelzer, W. W., and Blum, A.: Adrenal Cortical Insufficiency in Infants With Adrenogenital Syndrome, J. PEDIAT. 35: 344, 1949.
11. Cameron, A. T.: Recent Advances in Endocrinology, ed. 6, Philadelphia, 1947, The Blakiston Company, p. 225.
12. Blackman, S. S.: Concerning Function and Origin of the Reticular Zone of Adrenal Cortex; Hyperplasia in Adrenogenital Syndrome, Bull. Johns Hopkins Hosp. 78: 180, 1946.
13. Goldzieher, M. A.: The Adrenal Glands in Health and Disease, Philadelphia, 1944, F. A. Davis Company.
14. Collis, W. R. F., and Majekodunmi, M. A.: The Premature Infant, Management and Prognosis, Brit. M. J. 1: 31, 1943.
15. Hislop, W. A.: Treatment of Marasmus by Injection of Extract of Adrenal Cortex, Lancet 2: 308, 1938.

16. Akerren, Y.: Shock in Premature Children, Acta. pædiat. **32**: 804, 1945.
17. Miller, R. A.: Observations on Gastric Acidity During the First Month of Life, Arch. Dis. Child. **16**: 22, 1941.
18. Jaudon, J. .: Hypofunction of the Adrenals During Early Life, J. PEDIAT. **29**: 696, 1946.
19. Goldzieher, M. A., and Gordon, M. B.: The Syndrome of Adrenal Hemorrhage in the Newborn, Endocrinology **16**: 165, 1932.
20. Waterhouse, R.: A Case of Suprarenal Apoplexy, Lancet **1**: 576, 1911.
21. Friderichsen, C.: Nebennierenapopleie bei Kleimen, Jahrb. f. Kinderh. **87**: 109, 1918.
22. Ceballos, A., Frank, T. V., and Simpson, W. F.: The Waterhouse-Friderichsen Syndrome, J. PEDIAT. **27**: 281, 1945.
23. Kunstadter, R. H.: The Waterhouse-Friderichsen Syndrome, Arch. Pediat. **56**: 489, 1939.
24. Frior, W. M.: Adrenal Hemorrhage in Children, South. M. J. **30**: 306, 1937.
25. Rich, A. R.: Peculiar Type of Adrenal Coritcal Damage Associated With Acute Infections, and Its Possible Relation to Circulatory Collapse, Bull. Johns Hopkins Hosp. **74**: 1, 1944.
26. Seyle, H.: The General Adaptation Syndrome of the Diseases of Adaptation, J. Clin. Endocrinol. **6**: 117, 1946.
27. Thomas, H. M., Jr.: Treatment of Fulminating Meningococcic Infections, Bull. U. S. Army M. Dept. **73**: 78, 1944.
28. Grollman, A.: The Adrenals, Baltimore, 1936, William & Wilkins Company.
29. Neugebauer, J.: As quoted by Soffer, L. J., Diseases of the Adrenals, Philadelphia, 1946, Lea & Febiger, p. 109.
30. Jaudon, J. C.: Personal communication.
31. Marchand, F.: Virchows Arch. f. path. Anat. **92**: 11, 1883.
32. Glynn, E. E.: The Adrenal Cortex, Its Rests and Tumors, Quart. J. Med. **5**: 167, 1912.
33. Wilkins, L.: A Feminizing Adrenal Tumor Causing Gynecomastia in a Boy Five Years Contrasted With a Virilizing Tumor in a Five-Year-Old Girl, J. Clin. Endocrinol. **8**: 111, 1948.
34. Young, H. H.: Congenital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, 1937, Williams & Wilkins Company.
35. Bartrud, T. E., and Thompson, W. A.: Congenital Hyperplasia of the Adrenals, Staff Meet. Bull., Hosp. U. Minn. **15**: 25, 1943.
36. Allibone, M.D., Baar, H. S., and Cant, W. H. P.: The Interrenal Syndrome in Childhood, Arch. Dis. Child. **22**: 210, 1947.
37. Chenoweth, B. M.: Dysfunction of the Adrenal Gland in Infancy, South. M. J. **41**: 307, 1948.
38. Dijkhuizen, R. K., and Behr, R.: Adrenal Hypertrophy in Infants, Acta Pædiat. **27**: 279, 1940.
39. Pantos, T.: Personal communication. (To be reported.)
40. Wilkins, L.: Advances in Pediatrics, vol. 3, New York, 1948, Interscience Publishers, Inc.
41. Wilkins, L., and Lewis, R. A.: The Effect of Adrenocorticotrophic Hormone in Congenital Adrenal Hyperplasia With Virilism and in Cushing's Syndrome Treated With Methyl Testosterone, J. Clin. Investigation **28**: 394, 1949.
42. Butler, W. M., Ross, R. A., and Talbot, N. B.: Probable Adrenal Insufficiency in an Infant, J. PEDIAT. **15**: 831, 1939.
43. Wilkins, L., Fleischmann, W., and Howard, J. E.: Macrogenitosomia Praecox Associated With Hyperplasia of the Androgenic Tissue of the Adrenal and Death From Corticoadrenal Insufficiency, Endocrinology **26**: 385, 1940.
44. Thelander, H. E., and Cholffin, M.: Congenital Adrenal Cortical Insufficiency Associated With Macrogenitosomia, J. PEDIAT. **18**: 779, 1941. Follow up: Thelander, H. E., and Cholffin, M.: J. PEDIAT. **29**: 213, 1946.
45. Darrow, D. C.: Congenital Adrenal Cortical Insufficiency With Virilism, Yale J. Biol. & Med. **16**: 579, 1944.
46. Levine, S. Z.: Conference at the New York Hospital, J. PEDIAT. **34**: 768, 1949.
47. Di Ruggiero, and Jolly, A.: Vomissements graves au Nourrisson et Hypertrophie des Surrenales, Ann. d'anat. path. **15**: 332, 1938.
48. Skelton, M. O.: Bilateral Adrenal Hypertrophy in Infancy, Arch. Dis. Child. **20**: 135, 1945.
49. Cahill, G. G.: The Adrenogenital Syndrome and Adrenal Cortical Tumors, New England J. Med. **218**: 803, 1938.
Cahill, G. G.: Adrenocortical Tumors, Surg., Gynec. & Obstet. **62**: 287, 1936.
50. Moore, F. P., and Cermak, E. G.: Adrenal Cysts and Adrenal Insufficiency in an Infant With Fatal Termination, J. PEDIAT. **36**: 91, 1950.
51. Provenzano, R. W.: Adrenocortical Hypoplasia in the Newborn Infant, New England J. Med. **242**: 87, 1950.

USE OF CHLOROMYCETIN IN INFECTIONS

I. In Nonbacterial (Atypical Undifferentiated Respiratory Infections)

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THE introduction of Chloromycetin in 1947[1] promised to further extend the range of antibiotics against infectious agents. In short order its usefulness was proved in rickettsial diseases,[2] typhoid fever,[3] and undulant fever.[4] Since laboratory studies, in vitro and in animals, also revealed antibiotic action upon certain Shigella infections, *Klebsiella pneumoniae, Vibrio comma, Bacillus pertussis,* and a number of gram-negative organisms,[1, 5] a clinical trial of Chloromycetin in chlorea, dysentery, Salmonella infections, Friedländer's pneumonia, whooping cough, urinary infections, and other infections seemed indicated. Laboratory investigations on viral agents have revealed[2a] that Chloromycetin is effective against at least two viruses, those of psittacosis and venereal lymphogranuloma, but ineffective against other viruses tested, notably influenza, variola, and Japanese encephalitis. A trial of Chloromycetin in diseases presumably of viral origin would thus appear to have some basis.[2]

A preliminary in vitro study of bacterial sensitivity to Chloromycetin confirmed the fact that the gram-positive group of organisms are many times more sensitive to penicillin on a weight basis. Recent extensive investigations,[5b] however, have not only confirmed that gram-positive cocci are moderately sensitive to Chloromycetin,[5a] but that their growth is inhibited by concentrations within obtainable therapeutic levels. Pneumococci, of different types, and four strains of *Streptococcus hemolyticus* were inhibited in growth by Chloromycetin in concentration of from 1 to 2.5 μg per cubic centimeter. Inhibition of Staphylococcus required a higher concentration of Chloromycetin, but still within therapeutic range. A concentration of Chloromycetin (1 to 10 μg) was required to inhibit the growth of various strains of *Staphylococcus albus, Staphylococcus citreus,* and *Staphylococcus aureus,* the last requiring the greatest concentration (5 to 10 μg per cubic centimeter), a blood level obtainable with proper dosage. The gram-negative group was much more sensitive to Chloromycetin than to penicillin, requiring a Chloromycetin concentration of from 1 to 4 μg for growth inhibition. Among those so sensitive was the typhoid-dysentery group, twenty-three Salmonella types, most coliform organisms, and *Aerobacter aerogenes,* the latter a very resistant organism in urinary infections. Animal experiments indicated that the action of Chloromycetin in Salmonella infections was bacteriostatic rather than bacteriocidal.[6]

Chloromycetin has such a disagreeably bitter taste that the ingestion of a solution is provocative of nausea and vomiting. Administered in capsule form, this unpleasant taste and its side effects are not experienced. Older children who can swallow capsules intact have no difficulties, and present no problems. Infants and young children unable to swallow the capsule must perforce take the drug in some vehicle. We have achieved the best results by mixing the

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powder in chocolate syrup, sweet cherry, or raspberry syrup. Little vomiting ensues when Chloromycetin has its taste so disguised. A brief trial was made of rectal suppositories in young infants, but the results were unsatisfactory. In hot weather the suppositories would tend to stick to the nurse's fingers or to the perianal region of the baby. Often, when successfully inserted, the suppositories were expelled and provoked frequent bowel movements.

Originally our dosage schedule was 50 mg. per kilogram per day with an initial loading dose of 25 mg. per kilogram. Experience soon showed that better results were obtainable with a dosage of 100 mg. per kilogram per day until the temperature subsided, followed by a maintenance dose of 50 mg. per kilogram until the temperature was normal for 4 days. An initial loading dose of 50 mg. per kilogram per day, divided in two or three doses at hourly intervals, was instituted in several infections. Blood levels were taken in several cases; the original dosage of 50 mg. per kilogram revealed levels of from 5 to 10 μg in one hour which fell to 2 to 4 μg per cubic centimeter of blood serum in four hours. If the drug was discontinued too soon (less than 6 to 7 days), relapses or recurrences were noted in some instances, an observation noted in infections treated with Chloromycetin.[7]

The total amounts administered to the children treated varied from 2 Gm. to 20 Gm. We encountered no toxic manifestations, no cutaneous or nervous phenomena, no apparent involvement of the liver or spleen, no gastrointestinal symptoms. Blood counts showed no effect on the hemoglobin, red cells, white cells, or platelets. Routine urinary examinations showed no abnormal findings. This lack of toxicity of Chloromycetin has been previously noted.[5, 8]

The largest group treated with Chloromycetin was in the category of atypical respiratory infections, abacterial in origin, a group which has not been benefited by specific therapeutic agents, with the exception of aureomycin in atypical primary pneumonia.

The investigations of the past few years by the Commission on Acute Respiratory Diseases, have demonstrated that the prevailing acute respiratory disease, excluding the common cold, is of nonbacterial origin in well over 75 per cent of cases. Different syndromes were recognized on the basis of the clinical picture, bacteriologic findings and evidence of experimental transmission, and they were classified into these groups:

1. Exudative tonsillitis and pharyngitis due to *Str. hemolyticus*, which comprised a small fraction of the cases.
2. Exudative tonsillitis with the findings of hemolytic streptococci in the throat but no streptococcal antibodies, a relatively normal white blood count, and in general a less severe clinical picture. This form of tonsillitis was not attributed to the Streptococcus but to a filterable agent.
3. An exudative tonsillitis and pharyngitis, with no demonstrable respiratory pathogens, but transmissible by filtered nasopharyngeal washings.
4. By far the most common form was an acute respiratory infection characterized by fever of several days' duration, moderately severe systemic symptoms with a prominence of hoarseness and cough, sometimes accompanied by chest pain, while nasal symptoms, when present, were not conspicuous. This most comon form of acute respiratory infection, nonbacterial in origin, was

designated Undifferentiated Acute Respiratory Disease. Because of the clinical similarity to acute influenzal infections, antibody studies were made but revealed no change of the titer of the influenza antibodies during and after the disease. Similarly the survey of the prevalent acute pulmonary infections proved that there were relatively few bacterial pneumonias in contrast to the frequently encountered primary atypical pneumonias. These findings indicate that the prevailing abacterial acute respiratory infections should no longer be called atypical, a misleading term (for the clinical pattern is characteristic), and it is now the typical acute respiratory infection. The diagnosis of abacterial or undifferentiated acute respiratory disease is made on the basis of the clinical picture, a relatively normal white blood count, absence of significant respiratory pathogens, roentgenologic pulmonary findings, aided by a process of exclusion.

Our experience with acute respiratory infections in recent years, and in this study, has been similar to the findings of the Acute Respiratory Commission. The acute forms of respiratory infection, noninfluenzal, revealed no bacterial pathogens with relatively normal blood counts. These patients were acutely ill with a disease process characterized by a tendency to extend to the bronchopulmonary tree, with or without the features of atypical pneumonia. A number of cases characterized by predominance of symptoms of involvement of the laryngotracheobronchial tract, often with croup, seem to fall into an intermediate group. Our investigations indicated that these latter cases fall into the category of "virus" croup, or "virus" tracheobronchitis, as recently reported,[10] probably the most alarming form of infectious croup now encountered.

The question arises as to whether this form of laryngotracheobronchitis is an extension to the bronchial tree of an undifferentiated acute respiratory infection. Our opinion is to the contrary, for the predominating symptomatology is different, as is the therapeutic response to Chloromycetin. The Commission on Acute Respiratory Disease has shown that there are at least two different filterable agents or viruses, other than influenza, responsible for the abacterial respiratory infection now prevalent. The causative agent of primary atypical pneumonia was also different from those of the common cold and the undifferentiated respiratory disease, with no cross immunity. We have therefore, classified our series of acute respiratory infections into three groups:

1. Acute Undifferentiated (Abacterial) Repiratory Disease
2. Acute Undifferentiated ("Virus") Laryngotracheobronchitis
3. Atypical or Abacterial Pneumonia

In our cases bacteriologic studies yielded no significant pathogens in the nasopharyngeal or tracheobronchial secretions or exudates. The white blood counts uniformly were low, with lymphocytosis rather than polynucleosis. Cold agglutinins and heterophile antibodies were also determined. Roentgenologic studies were routinely performed to determine the presence of pulmonary infiltrations. While laboratory studies were proceeding to determine the nature of the respiratory infection, penicillin was given parenterally in adequate dosage for at least forty-eight hours. Only if our criteria of abacterial infection were satisfied, and if there was failure or response to penicillin, or sulfa drugs and penicillin, was Chloromycetin administered.

Eight patients with upper-respiratory infection, drawn from private practice, since they were uncomplicated, were treated with Chloromycetin. They

ranged in age from 6 months to 18 years. Clinically they were characterized as a group, by fever, systemic symptoms, such as headache, and malaise, and signs and symptoms of involvement of the upper-respiratory tract with negative pulmonary findings. The leucocyte count was low or normal with a tendency to lymphocytosis. Nasopharyngeal cultures, taken in some cases, did not reveal any significant pathogens. These findings were similar to those of the Respiratory Commission's syndrome, undifferentiated acute respiratory infection.[9] Administration of penicillin, in some cases preceded by or concomitantly with sulfa drugs, produced no demonstrable effect. Chloromycetin was given in two cases because of hyperpyrexia of between 106° F. to 107° F. The temperature dropped sharply to normal within twenty-four to forty-eight hours. In other cases Chloromycetin was given because of a persistent temperature, sometimes as long as six weeks. Within forty-eight hours after the administration of the drug the temperature became normal. The appearance of the nose and the throat, however, did not resume normalcy for days after the temperature became normal. In such cases a cough was likely to persist for a similarly long period. It may be advisable in prolonged infections to administer Chloromycetin for a longer period and in higher dosage.

CASE 1.—A. L., 18 years old, had a chief complaint on Sept. 7, 1949, of headache, dizziness, and malaise. Fever was 101° F. to 102° F. Patient had had a five days' cough.

Examination revealed flushed facies, a moderately red throat, and nasal mucosa. There was no enlargement of the cervical glands. Heart and lungs were negative by examination and fluoroscopy. Abdominal, neurological, and the rest of the examinations were negative.

Hemoglobin was 80 per cent, white blood count 8,250, polymorphonuclears 48 per cent, lymphocytes 50 per cent, monocytes 2.

Diagnosis was upper-respiratory infection, probably atypical or viral.

Therapy prescribed was Chloromycetin given 3 Gm. the first day, after which the temperature dropped to normal and the symptoms abated; 2 Gm. daily were given for four more days, when examination was completely negative.

Examination on September 9 showed improvement, and no fever. On September 13 the patient was symptom-free and had had no fever for 6 days; Chloromycetin was stopped. Examination was negative. The patient had gained 2½ pounds, felt well, and ate well.

CASE 2.—W. R., for the last six months, had been subject to febrile episodes of acute nature, the temperature varying from 100° F. to 102° F.

The patient was brought to me on July 27, 1949, with a story of a fluctuating temperature for three weeks; the patient had been given sulfa and penicillin in adequate dosage without avail.

X-rays of the chest had been negative; intradermal tuberculin test was negative; temperature recorded in the office was 101.8° F. Examination was negative except for enlarged red tonsils, redness of the pharynx, and swelling and redness of the nasal mucosa.

Hemoglobin was 65 per cent, white blood count 10,250, polymorphonuclears 31, lymphocytes 66, monocytes 1, eosinophiles 2, sedimentation rate 7 mm. in forty-five minutes. Fluoroscopic examination revealed negative pulmonary findings. X-ray of chest showed no pulmonary involvement.

Therapy consisted of penicillin lozenges and penicillin inhalation treatment (nose and throat) which was tried for 4 days with no effect. On August 1, Chloromycetin was given, dosage 1½ Gm. first day and 1 Gm. daily thereafter.

The temperature dropped to normal within thirty-six hours and has remained so.

Seven patients with laryngotracheobronchitis were treated with Chloromycetin. This group ranged in age from 10 months to 6 years. Clinically the

patients were characterized by fever, a distressing cough, signs of tracheobronchitis with no pulmonary infiltration revealed by x-ray, except in one infant. Bacteriologic studies revealed no significant pathogens which suggested that these cases belong in the group of "virus" croup.[10] Two infants had obstructive laryngitis with hoarseness, stridor, suprasternal retraction, dyspnea, and cyanosis. These infants with obstructive breathing were not materially helped by penicillin but seemed to benefit by Chloromycetin. In some cases the temperature which had become low grade, was unaffected, but the laryngeal symptoms and cough lessened considerably, and the breathing became easier. In other cases the temperature gradually subsided in from 2 to 3 days, but the cough was likely to persist for days. The general clinical impression was that Chloromycetin exerted a favorable effect upon the tracheobronchitis including the laryngeal component. Some patients seemed to respond quickly and rather completely except for the cough, while others improved gradually. It may will be that with our new increased dosage these suggestive results may become more definite and decisive, for we now feel that the dosage may have been too small and hence inadequate.

CASE 9.—J. B., a 16-month-old boy, had coryza for 5 days; dyspnea and fever for one day. The patient was apparently well although he had had frequent episodes of laryngitis for many months, until one week prior to the admission when he developed a rhinorrhea and slight cough. On the day of admission he became dyspneic, had a croupy cough, with frequent choking spells. Before admission, the patient was given 300,000 u. of procaine penicillin, aspirin, syrup of ipecac, and steam with no appreciable effect.

On admission the child appeared to be in acute respiratory distress, with substernal and subcostal retraction; he had marked hoarseness, was quite restless and had inspiratory stridor. His tonsils were markedly enlarged and reddened; the epiglottis could be visualized as reddened but not edematous. There were many course râles heard over both chests.

The laboratory findings showed a slight trace of acetone in the urine; 84 per cent hemoglobin, red blood count 4.1 million, 8,300 leucocytes, with 36 polymorphonuclears, 4 stab cells, 45 lymphocytes, and 10 monocytes. Erythrocyte sedimentation rate was 12 mm, per hour. X-ray examination showed a few scattered infiltrations in both lungs, and a lateral view of the larynx showed a soft tissue swelling behind the air column in the pharynx and larynx. Cultures taken from the nose showed nonhemolytic streptococci, *Streptococcus viridans*, and *Micrococcus catarrhalis*. Throat cultures showed *Staph. albus*.

On admission the patient was laryngoscoped and it was ascertained that the airway was unobstructed above the larynx, but a large quantity of thick mucopus could be seen coming up from the subglottic region of the trachea. The patient was placed on steam, syrup of ipecac, and penicillin, 50,000 u. every three hours, and the temperature dropped to 100° F. soon afterward. The hoarseness persisted and the obstructive breathing seemed unabated, with vomiting of large quantities of thick mucopus. On the ninth hospital day, the patient was placed on Chloromycetin 80 mg. every hour for three doses, and then 80 mg. every three hours afterward. Improvement of the hoarseness and dyspnea followed. The patient was discharged as improved on the seventeenth hospital day.

CASE 10.—R. M. S., a 2½-year-old girl, had an initial complaint of pain in the left calf 10 days before admission. There was no swelling or local inflammatory signs. On the following day the patient developed diarrhea which ceased without therapy. Five days before admission the patient had developed a temperature of 105° F. with a reddened pharynx. She was given 100,000 u. of penicillin daily for 3 days. On the day before admission the patient developed a severe urticarial rash over the entire body, with a papular eruption over the abdomen and extremities.

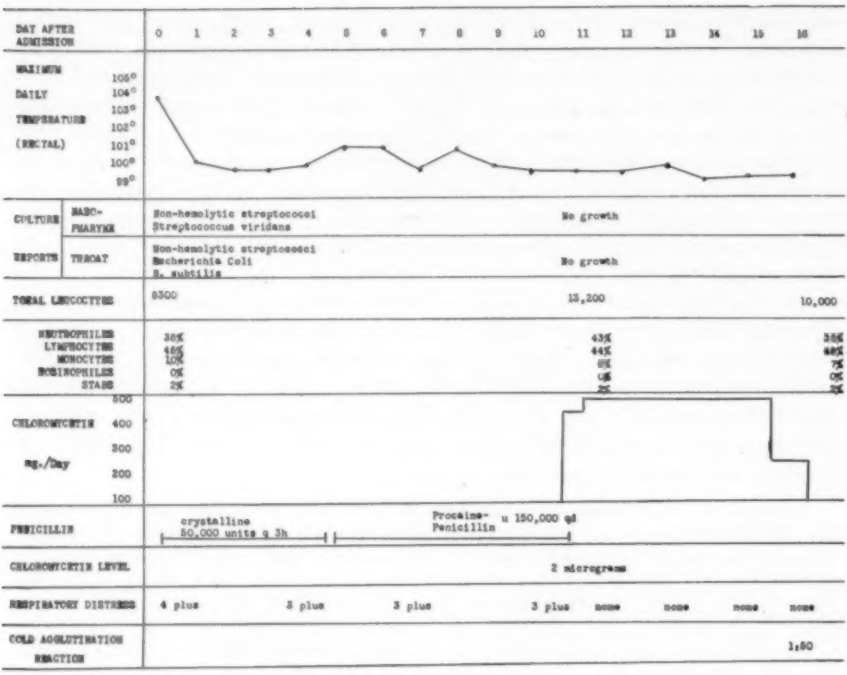

Chart 1.—Case 9, laryngotracheobronchitis. Patient is J. B., a male infant, aged 16 months, weight 13 kg.

Physical examination showed the child to be acutely ill and somewhat lethargic. There was redness of the drum membranes and ulcerations in the pharynx, buccal mucosa, and the tonsils, which were markedly hypertrophied. There was some exudate on the right tonsil. The lymph nodes of the anterior and posterior cervical chains were enlarged. There were few rhonchi noted in the chest, but the examination of the lungs was otherwise negative. There was a systolic murmur at the apex and pulmonary area. The liver descended to 3 cm. below the costal margin and the spleen was palpable 2 cm. below the costal margin. There was a marked enlargement of the axillary and inguinal nodes bilaterally. The skin of the body was covered with a diffuse urticarial rash and papular eruption over the extremities and abdomen.

Urine examination, on admission, was negative. The blood hemoglobin was 64 per cent with 3 million red blood cells, 7,400 white blood cells, 36 per cent polymorphonuclears, 24 stab cells, 30 per cent lymphocytes, and 10 per cent monocytes. Culture of the nose and throat secretions showed *Staph. albus* and *Staph. aureus*. Heterophile antibody test was negative. Blood culture was negative, cold agglutinins were negative, and agglutination tests against typhoid, paratyphoid, typhus, brucellosis, and tularemia were negative.

Course of patient in hospital:

The temperature of the patient on admission was 102.4° F. and rose to 104.5° F. in four hours, in spite of massive doses of penicillin. On the second hospital day Chloromycetin was instituted in doses of 100 mg. per kilogram body weight for the first twenty-four hours (half initially) followed by 50 mg. per kilogram per day for the second to the seventh hospital days. Within twenty-four hours after Chloromycetin therapy the temperature dropped to normal, the rash disappeared almost completely, and the mouth lesions improved. The lym-

phatic glands remained enlarged. On the sixth hospital day the heterophile antibody titer was reported as being positive in dilutions of 1:200, but absorption studies were negative for mononucleosis. A subsequent heterophile reaction was negative on the twelfth hospital day. The patient was discharged on the fifteenth hospital day completely cured.

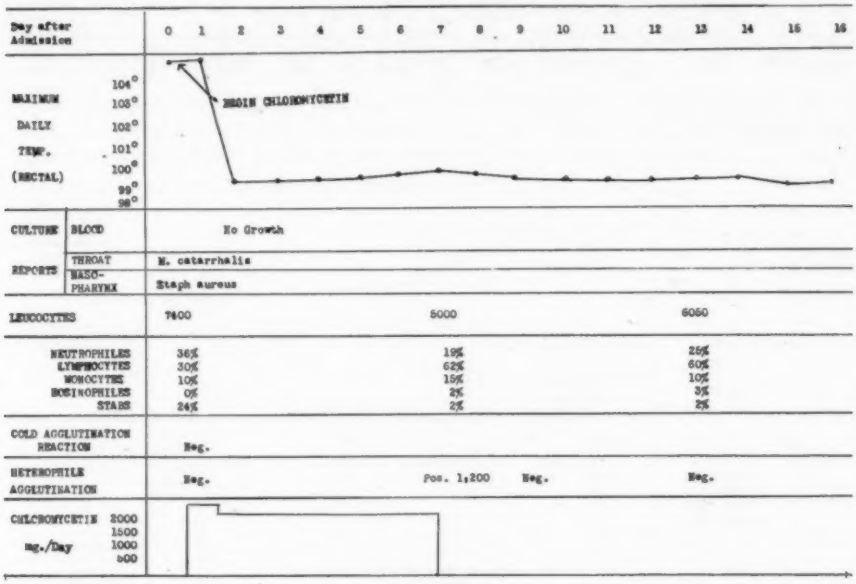

Chart 2.—Case 10, laryngotracheobronchitis. Patient is R. M. S., a female infant, aged 3 years, weight 14 kg.

CASE 11.—B. J. C., a 10-month-old girl, was well until two weeks before admission when she developed a fever (101° F.), coryza, sore throat, and slight dyspnea. Penicillin was given without effect, and two days before admission she awakened at night with a marked hoarseness and difficulty in breathing. On the night before admission, the cough became croupy and the breathing noisy.

On physical examination the patient had labored breathing with considerable stridor. The tonsils and peritonsillar areas were markedly reddened and edematous. The epiglottis was not edematous. The chest was somewhat dull at the right base, and there were numerous course râles and rhonchi, which seemed to be transmitted from the larynx. The hemoglobin was 67 per cent with a red blood count of 4.5 million. There were 12,350 white blood cells, with 35 per cent polymorphonuclears, 7 stab cells, 50 lymphocytes, and 7 monocytes. The urine was negative. The culture of the nasopharynx showed *Staph. albus*.

X-rays taken on admission showed a slight amount of emphysema of both lungs, but no infiltration or consolidation. On the day after admission, the patient was placed on 125 mg. of Chloromycetin every two hours for three doses, and 125 mg. every four hours thereafter. The stridor completely cleared on the third hospital day, and the patient seemed clinically much improved. Slight hoarseness still persisted until discharge on the ninth hospital day. Temperature remained normal after the third day. A Chloromycetin level taken on blood withdrawn one hour after last dose was 2 μg per cubic centimeter.

In eleven cases of atypical pneumonia with characteristic pulmonary infiltrations, clinical picture, and laboratory findings,[9] the response to Chloromycetin

was striking in ten cases out of eleven. Whereas the previous exhibition of penicillin and sulfa drugs had been without effect, the administration of Chloromycetin resulted in a precipitous drop in temperature, and a concomitantly rapid improvement of the clinical picture. Infants who were dyspneic, cyanotic, and in some cases croupy, within twenty-four to forty-eight hours enjoyed a normal temperature and acted normally, relieved of cyanosis and dyspnea. The physical signs, x-ray findings, and the cough disappeared in a

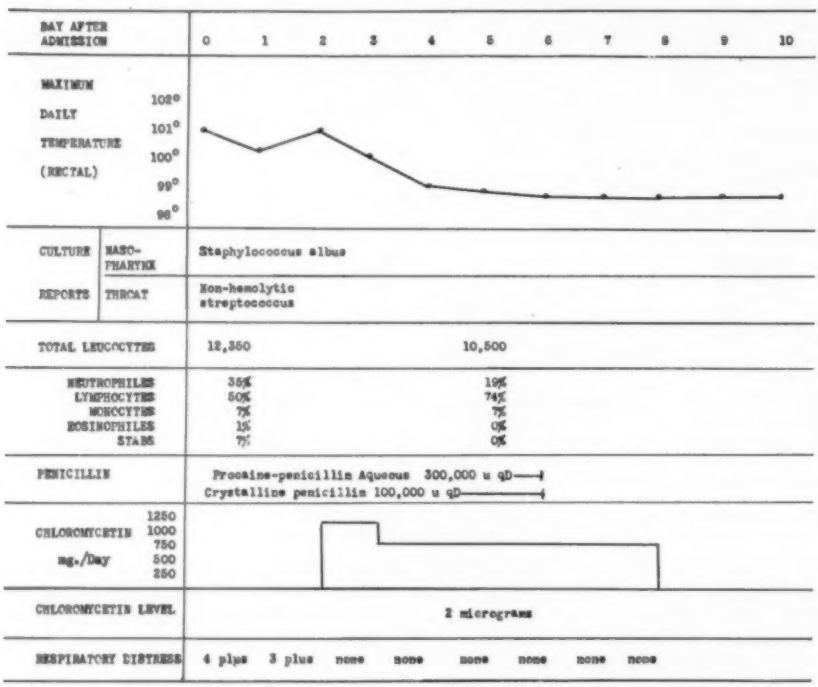

Chart 3.—Case 11. larygotracheobronchitis. Patient is B. J. C., a female infant, aged 10 months, weight 8.1 kg.

few days. One infant was convalescing from his pneumonic condition, still under Chloromycetin treatment, with a normal temperature, normal breathing, and a virtual disappearance of physical signs, but with a persistent cough. Three days after his temperature was normal, and while still on the maintenance dose of Chloromycetin, this infant developed suppurative otitis media with a rise in temperature. This secondary infection responded to penicillin, which had been useless at the onset of the original infection. Such cases suggest that combined therapy with antibiotic agents may prove very useful in children prone to secondary bacterial infections, if prevalent.

We have encountered trying experiences with infants affected with congenital cardiac conditions, resulting in excessive pulmonary blood supply and

pulmonary congestion. These infants, during the winter, when respiratory infections are common, are very prone to contract tracheobronchial infections with pulmonary involvement, and become desperately ill. They not only become dyspneic and cyanotic, but may rapidly succumb to heart failure. We had the same difficulty in an infant afflicted with Cooley's anemia with resultant heart failure. Trial of penicillin effected no improvement in given cases, but the administration of Chloromycetin produced gratifying effects. The fever subsided, the dyspnea and cyanosis improved to the point of comfort, and a desperately ill baby returned to his former status. In such cases of heart disease complicated by bronchopulmonary infections of an atypical nature, Chloromycetin was a very valuable, if not lifesaving agent.

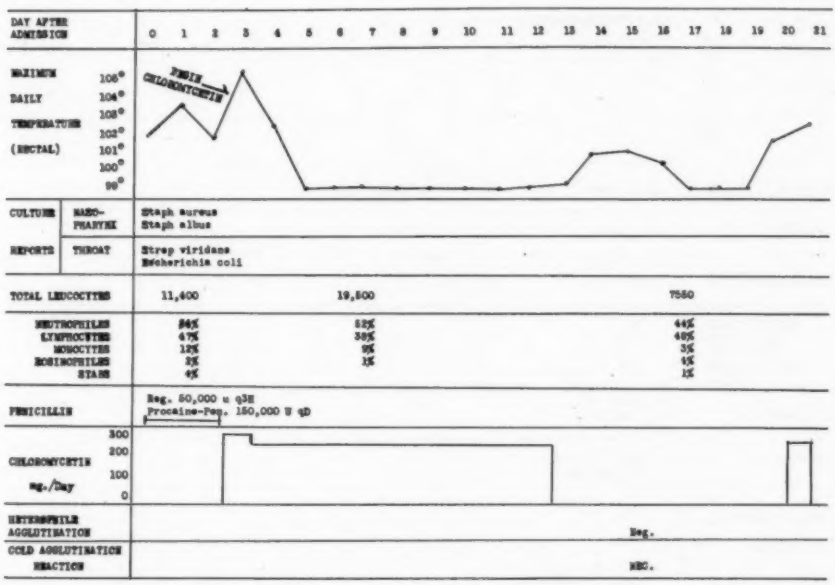

Chart 4.—Case 17, congenital cardiac with bronchitis and atypical pneumonia. Patient is I. S., a male infant, aged 3 months, weight 3.1 kg.

CASE 17.—I. S., a 3-month-old male infant, born at term, weighing 5 pounds, 7 ounces. The child was cyanotic at birth, but at one day of age the child developed a respiratory infection with a temperature of 102° F. that subsided in twenty-four hours with penicillin therapy. During the third week of life the patient became dyspneic, and examination by family physician disclosed a loud cardiac murmur. At the eighth week the patient developed a bronchopneumonia with high fever and cyanosis. Treatment with sulfadiazine and penicillin was ineffective but the patient responded to aureomycin with prompt clearing of the lesion. One week before admission to this hospital the infant developed diarrhea with a 1½ pound weight loss.

On admission the patient had a slight cyanotic tinge and appears to be in acute respiratory distress. The examination of the chest revealed diminished breath sounds and fine and sibilant râles at the end of inspiration in the left lower chest posteriorly. There

was dullness on the left side anteriorly to the anterior axillary line. The heart rate was rapid (160) with a loud systolic murmur and thrill at the third left intercostal space. The liver was 3 cm. below the costal margin; and the spleen was not felt. On admission the urine was normal. The blood count revealed 97 per cent hemoglobin, 3.7 million red blood cells, 11.400 white blood cells, 34 per cent polymorphonuclears, 4 stab cells, 47 per cent lymphocytes, and 2 eosinophiles. The carbon dioxide content was 48.9 volumes per cent.

The temperature was 102.2° F. on admission. X-ray examination showed increased peribronchial markings bilaterally, with infiltrations in both lung fields. The cardiac silhouette was globular and markedly enlarged, with convexity of the pulmonic segment. The electrocardiogram demonstrated right axis deviation. Nose and throat culture revealed *Staph. albus* and *Staph. aureus.*

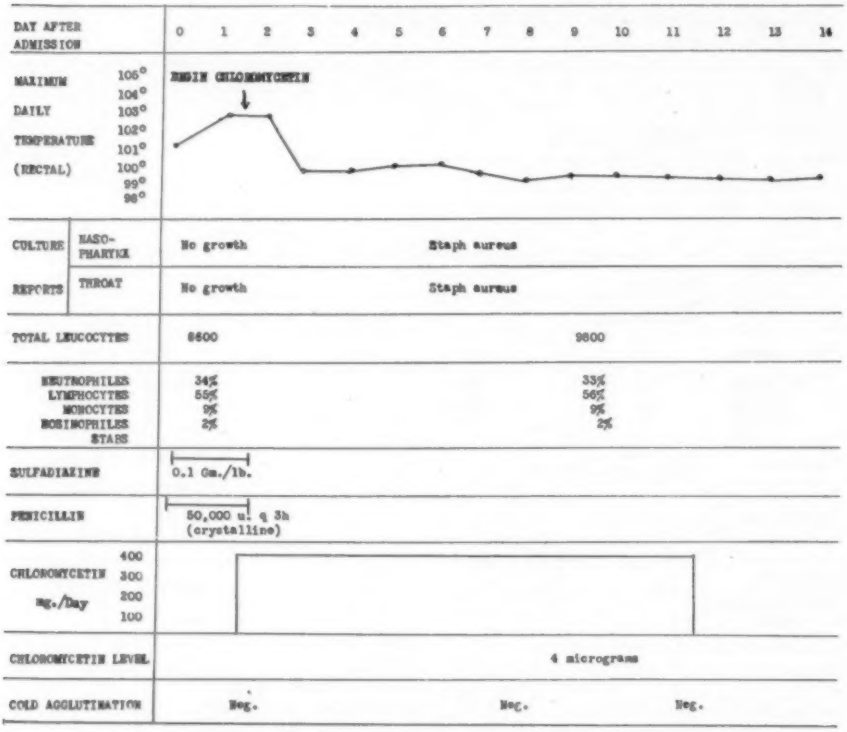

Chart 5.—Case 18, atypical pneumonia. Patient is E. N., a girl, aged 6 years, weight 24 kg.

The patient was given 300,000 u. of procaine penicillin daily for 3 days with no effect. Chloromycetin was begun on the fourth day in doses of 100 mg. per kilogram with partial clearing of the râles in the 3 days and drop in temperature to normal in two days with marked improvement in respiratory symptoms. The Chloromycetin was stopped after 7 days and shortly thereafter (3 days) the temperature once again rose to 102.4° F. and râles reappeared. Three days thereafter the patient developed swelling around the eyes, and subsequently peripheral edema and pulmonary edema, and the patient died of heart failure.

CASE 18.—E. N., a 6-year-old girl, was well until 3 days before admission, when she began to cough frequently, and developed a temperature of 102° F. on the following day.

The cough usually followed feedings, and occasionally produced severe vomiting spells. The cough became productive of a frothy white sputum and the temperature rose to 103.5° F. on the day of admission.

On examination, there was noted dullness over the lower lobes of both lungs posteriorly, with coarse rhonchi heard throughout both lung fields with medium, moist râles over the lower lobe on the left side posteriorly from the infrascapular region downward, also in the left-upper lobe and right-lower lobe anteriorly.

The laboratory findings showed a negative urine examination. The erythrocytes count was 4.5 million, with 84 per cent hemoglobin, 6,350 leucocytes, polymorphonuclears 41 per cent, stab cells 4 per cent, lymphocytes 46 per cent, and monocytes 9 per cent. The sedimentation rate was 10 mm. in one hour. The x-ray showed moderate number of infiltrations in the mesial portions of the lower lobes bilaterally. The cold agglutinin and heterophile antibody titers were negative. The throat culture showed nonhemolytic streptococcus and *M. catarrhalis.*

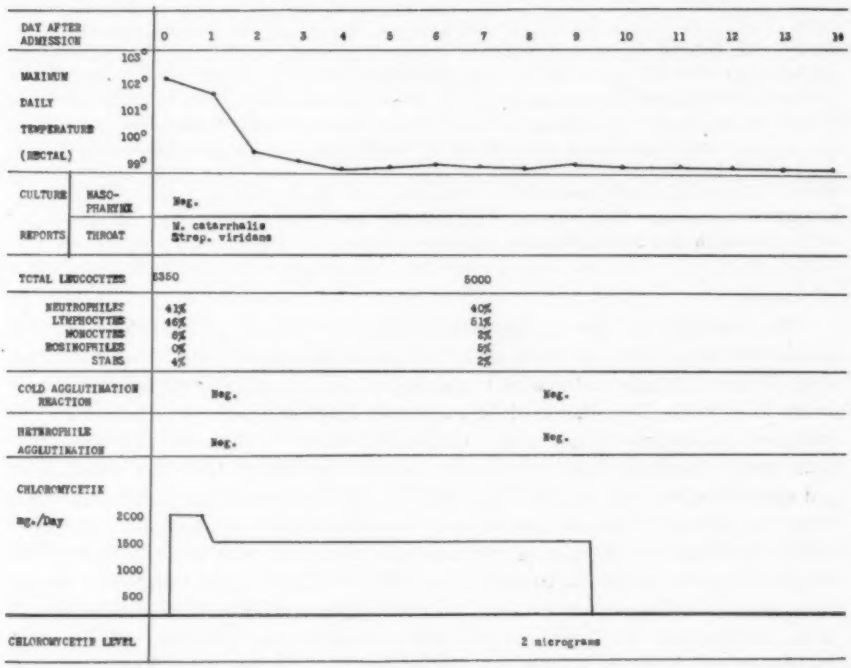

Chart 6.—Case 19, atypical pneumonia. Patient is R. T., a female infant, aged 2½ months, weight 5.5 kg.

On admission the patient was given Chloromycetin (250 mg. every hour for three doses, and then 250 mg. every four hours). The temperature dropped to normal in twenty-four hours, with marked decrease in the chest findings, in the left lower lobe particularly. An x-ray taken on March 9, showed definite clearing. The Chloromycetin was stopped on March 8, with marked improvement in the clinical condition. The patient was discharged on March 13, 1949.

CASE 19.—R. T., a 2½-month-old white girl, was admitted with a history of coryza, dyspnea, and fever for 2 days, when temperature rose to 103° F. She had suddenly begun

to cough heavily with a marked rhinorrhea, and difficulty in breathing. She choked on several feedings, with increasing cyanosis during the choking spells. She was heard to wheeze a great deal, and patient was finally brought to hospital, because the condition grew worse.

On admission, the patient was in acute respiratory distress, with marked pallor and slight cyanosis. The throat was markedly injected and dullness and moist râles were noted in both lung fields, with diminished breathing in the right lung field, at the base posteriorly. Blood count on admission showed 49 per cent hemoglobin (7.5 Gm.), 2.8 million red blood cells, 8,100 leucocytes, with 25 per cent polymorphonuclears, 9 per cent stab cells, 55 per cent lymphocytes, 10 monocytes, and 1 eosinophile. The cultures taken from the nose and throat were negative. X-ray of the chest showed infiltrations scattered throughout the right lower lobe. The heterophile antibody, and cold agglutinin titers were both negative on two occasions on March 25, and March 28.

Crystalline penicillin-G was given in 50,000 u. doses, every three hours, and sulfadiazine 1½ gr. per pound per twenty-four hours was given for twenty-four hours, without appreciable effect on the temperature or physical findings. Because of the poor response to chemotherapy and because the clinical condition worsened, a course of Chloromycetin was begun. An initial dose of 50 mg. in 20 per cent propylene glycol, by intramuscular injection was followed by 50 mg. orally every hour for two doses and then every three hours, until it was stopped on March 25. The patient's temperature dropped to a normal level in twenty-four hours, and remained normal for three weeks (until discharged). The physical findings in the chest subsided in forty-eight to seventy-two hours, and the x-rays repeated on March 19 and March 13, were completely negative. A Chloromycetin blood level on March 21, taken one hour after an oral dose of 50 mg. was 3 μg per cubic centimeter. The patient was discharged on the twentieth day after admission, clinically well.

DISCUSSION

The etiology of the nonbacterial respiratory infection prevalent in this section of the country in 1948 and 1949 is undetermined, but presumably of viral origin.[9] It may be unwise to assume a common etiological agent for our series since there is evidence of two or more filtrable agents implicated in the prevalent respiratory syndromes. Clinically, these atypical respiratory infections were classified into three types: upper-respiratory infection with fever and systemic symptoms, suggesting influenza and simulating the undifferentiated acute respiratory infection described by the respiratory Commission; laryngotracheobronchitis; and atypical pneumonia. The response of these infections to Chloromycetin after failure with penicillin, varied in these different forms of atypical respiratory infection. In the upper-respiratory, undifferentiated form, the response to Chloromycetin was immediate and striking, with prompt abatement of fever and systemic symptoms. In atypical pneumonia, after failure to respond to penicillin, the success of Chloromycetin was equally striking and speedy. The temperature subsided in a day or two, symptoms quickly disappeared, as did the pulmonary symptoms and signs and x-ray findings.

In the group with laryngotracheobronchitis, the response to Chloromycetin, after failure with penicillin, was not so decisive. While we gained the impression that there was an amelioration of the respiratory distress and a gradual subsidence of the fever and cough, the results did not indicate a definitely curative agent. Nevertheless, the partial success that we achieved seemed sufficient to warrant the use of Chloromycetin in abacterial (virus) laryngotracheobronchitis.[10] This is now the most common form, with a grave prognosis, because

of its tendency to extend to the bronchopulmonary tree, and its poor response to present therapeutic measures.[10]

Observations were also made in a group of fifteen cases characterized by a persistent cough of sufficient intensity and duration to suggest pertussis. It could be distinguished, however, from pertussis, because this paroxysmal cough followed a respiratory infection and fever, had a negative bacteriology with no leucocytosis and lymphocytosis, and no genuine whoop developed. This cough may have followed an acute undifferentiated respiratory infection. Chloromycetin, given for the relief of the distressing cough, was successful in causing its disappearance in from 2 to 4 four days.

Chloromycetin has a demonstrable antibiotic action on very few viruses.[1, 2, 3] Among these viruses against which it is ineffective in vitro is the influenza virus. Influenza antibodies of the blood serum was determined in several of our patients who responded to Chloromycetin. The level of the antibodies was so low as to indicate that these nonbacterial respiratory infections were not influenzal. It thus seems that Chloromycetin is effective in the treatment of acute nonbacterial respiratory infections of the various categories outlined by the Army Respiratory Commission,[9] which are due to two or more filterable agents, influenza, and the virus of the common cold playing no role in these respiratory syndromes.

In vitro studies have shown the sensitivity of the Pneumococcus, *Str. hemolyticus, Hemophilus influenzae, Klebsiella pneumoniae,* and to a lesser extent the Staphylococcus group of organisms. Furthermore, this sensitivity ranged from 1 to 10 μg of Chloromycetin per cubic centimeter of blood serum, a level obtainable without difficulty with appropriate dosage, in our experience and the experience of others.[8b, 11] Clinical confirmation of the striking effectiveness of Chloromycetin upon the respiratory pathogens, especially the gram-positive cocci has been overshadowed by the extreme sensitivity of the nasopharyngeal flora to penicillin. In view of the greater range of therapeutic efficiency of Chloromycetin, which affects bacteria as well as filterable agents, it seems to us that the therapeutic agent of choice in acute respiratory infections of undetermined origin, in the absence of an influenza epidemic or a common cold should be Chloromycetin, particularly if the bacteriology of the respiratory tract has not been determined.

SUMMARY

1. Chloromycetin has been used in the treatment of forty-one children suffering from nonbacterial or virus respiratory infections.

2. There were no toxic manifestations from the drug in our series with our dosage schedule.

3. It is our impression that Chloromycetin was effective in atypical pneumonia and in cases of nonbacterial or virus upper-respiratory infections with systemic symptoms.

4. Chloromycetin was only partially effective in laryngotracheobronchitis, but its use is recommended because of apparent amelioration of the respiratory distress.

5. Chloromycetin was successful in relieving a distressing and persistent cough, the sequel of an acute undifferentiated respiratory infection.

6. Administration in capsule form was a simple task in older children but impossible in infants. Vehicles are suggested for administration of the drug to infants.

7. Treatment should continue for 4 to 5 days after the temperature is normal.

8. Blood levels, with our dosage, ranged from 2 to 10 μg, an effective level, even for bacterial respiratory infections. Blood determinations are not routinely necessary in the treatment with Chloromycetin.

We are indebted to the bacteriologic laboratories of Beth Israel Hospital for bacterial studies and other laboratory determinations.

We are indebted to Parke, Davis & Company for supplying us with generous amounts of Chloromycetin and to their laboratories for the determinations of influential antibodies.

REFERENCE

1. Ehrlich, J., Bartz, Q. R., Joslyn, D. A., Smith, R. M., and Burkholder, P. R.: Chloromycetin, a New Antibiotic from a Soil Actinomycete, Science 106: 417, 1947.
2. a) Smadel, J. E., and Jackson, E. B.: Chloromycetin; Antibiotic With Chemo-Therapeutic Activity in Experimental and Viral Infections, Science 106: 418, 1947.
   b) Smadel, J. E., Woodward, T. E., Ley, H. L., Jr., Philip, C. B., Traub, R., Lewthwaite, R., and Savoor, S. R.: Chloromycetin Treatment of Scrub Typhus, Science 108: 160, 1948.
   c) Smadel, J. E., Leon, A. P., Ley, H. L., Jr., and Varela, G.: Chloromycetin in Treatment of Patients with Typhus Fever, Proc. Soc. Exper. Biol. & Med. 68: 12, 1948.
   d) Pincoffs, M. C., Guy, E. G., Lister, L. M., Woodward, T. E., and Smadel, J. E.: Treatment of Rocky Mountain Spotted Fever with Chloromycetin, Ann. Int. Med. 29: 656, 1948.
3. Woodward, T. E., Smadel, J. E., Ley, H. L., Jr., Green, R., and Mankikar, D. S.: Preliminary Report on the Beneficial Effect of Chloromycetin in the Treatment of Typhoid Fever, Ann. Int. Med. 29: 131-134, 1948.
4. Knight, V., McDermott, W., and Ruiz-Sanchoz, F.: Aureomycin and Chloromycetin; Use in Typhus, Typhoid, and Brucellosis, Presented at the Second National Symposium on Recent Advances in Antibiotic Research, Washington, D. C., April 12, 1949.
5. a) Smith, R. M., Joslyn, D. A., Grihzit, O. M., McLean, I. W., Jr., Penner, M. A., and Ehrlich, J.: Chloromycetin in the Biological Studies J. Bact. 55: 425, 1948.
   b) McLean, I. W., Schwab, J. L., Hillegas, A. B., and Schlingman, A.: Susceptibility of Micro-organisms to Chloramphenicol (Chloromycetin), J. Clin. Investigation 28: 953, 1949.
6. Seligmann, E., and Wasserman, M.: Action of Chloromycetin on Salmonella, Proc. Soc. Exper. Biol. & Med. 71: 253-255, 1949.
7. a) Smadel, J. E., Woodward, T. E., and Bailey, C. A.: Relation of Relapses in Typhoid to Duration of Chloramphenicol Therapy, J. A. M. A. 141: 2, 129, 1949.
   b) Woodward, T. E.: Chloromycetin and Aureomycin: Therapeutic Results, Ann. Int. Med. 31: 1, 53, 1949.
8. a) Ley, H. L., Jr., Smadel, J. E., and Crocker, T. A.: Administration of Chloromycetin in Normal Human Subjects, Proc. Soc. Exper. Biol. & Med. 68: 9, 1948.
   b) Guhzit, O. M., Fishken, R. A., Reutner, T. F., and Martino, E.: Chloramphenicol (Chloromycetin), An Antibiotic, Pharmacological and Pathological Studies in Animals, J. Clin. Investigation 28: 943, 1949.
9. a) Commission on Acute Respiratory Diseases: Clinical Patterns of Undifferentiated and Other Acute Respiratory Diseases in Army Recruits, Medicine 26: 441, 1947.
   b) The Bacteriological Findings in Undifferentiated and Other Acute Respiratory Diseases, ibid. 465.
   c) Experimental Transmission of Minor Respiratory Illness to Human Volunteers by Filter Passing Agents, J. Clin. Investigation 26: 957, 974, 1947.
   d) Reimann, H. A.: The Viral Pneumonias and Pneumonai of Probable Viral Origin, Medicine 26: 167, 1947.
10. Rabe, E. F.: Infectious Croup—Virus Group, Pediatrics 2: 415, 1948.
11. Recinos, A., Ross, S., Olshaker, B., and Twible, E.: Chloromycetin in Treatment of Pneumonia in Infants and Children, New England J. Med. 241: 733, 1949.

INFLUENZAL MENINGITIS TREATED WITH CHLOROMYCETIN

A Preliminary Report

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MENINGITIS caused by *Hemophilus influenzae* is a formidable disease of infancy and early childhood; 80 per cent of recorded cases occur in children under the age of 2 years.[1] A noncontagious sporadic disease of seasonal incidence, its occurrence seems to be associated with upper-respiratory tract infections in which *H. influenzae* is the causative agent.

Prior to 1936 the disease was reported as having a mortality of from 90 to 100 per cent. With the advent of sulfonamides there was a slight improvement in the mortality rate. Both Pittman[2] and Alexander[3] found sulfadiazine the most efficacious of these drugs in combating infections caused by *H. influenzae*. In 1939 Alexander[4] reported the use of rabbit serum effective against *H. influenzae*, type B. These two therapeutic agents in combination proved effective in the treatment of the disease. More recently Keefer,[5] Alexander,[6] and a number of others showed that in vitro and in vivo streptomycin is effective against hemophilus influenzal bacillus, type B, and the addition of streptomycin as a therapeutic agent further improved the outlook in this disease.

In 1949, Crook, Clanton, and Hodes[7] outlined a complex method of treatment for influenzal meningitis which combines the use of streptomycin, intrathecally and intramuscularly, with rabbit antiserum intravenously, sodium sulfadiazine intravenously and subcutaneously, and penicillin intramuscularly. Of 110 infants so treated, 79 per cent survived and 62 per cent recovered completely. Long and his associates[8] have felt that the drug of choice in severe cases is aureomycin in conjunction with sulfadiazine, stating in 1949 that the effect of Chloromycetin was undetermined.

The known effectiveness of Chloromycetin against gram-negative organisms together with the apparently good results obtained using Chloromycetin in the treatment of one case of influenzal meningitis (Fig. 1) which had failed to respond to therapy with streptomycin and sulfadiazine, led us to treat four additional patients with Chloromycetin alone.

Chloromycetin has been demonstrated in the spinal fluid within three hours after an average dose.[9] In each case an attempt was made to supply well over 60 mg. per kilogram body weight every twenty-four hours, since some of the drug might be lost by vomiting. When administered initially by gavage, however, the drug was retained, and after from thirty-six to forty-eight hours it was possible in each instance to administer the drug orally in Amphojel or jelly.

CASE REPORTS

Case 1.—R. M., a 6-month-old Mexican male infant (Fig. 2), was admitted to the hospital on Dec. 24, 1949. The onset of the present illness was marked by

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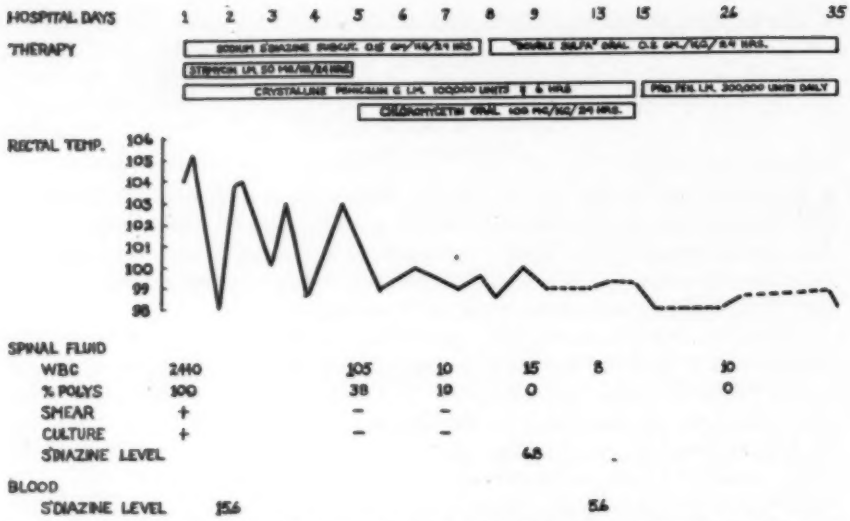
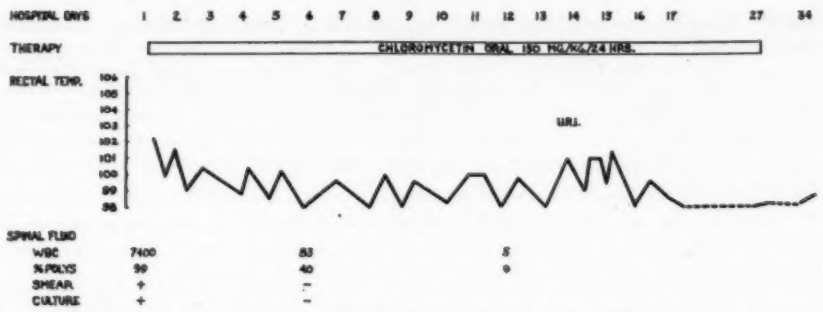


Fig. 1.—J. P., a 9-month-old Negro female infant weighing 9 kg., with type B *H. influenzae* meningitis.

fever of three days' duration and by left-sided convulsions, which became generalized by the afternoon of the day of admission. This child had a history of poor appetite and slow development. The only therapy prior to admission consisted of a vitamin "tonic." Physical examination revealed an acutely and chronically ill infant who was having clonic movements of the extremities. The anterior fontanel was tense and bulging. The fronto-occipital circumference was 40.5 cm. The skin was hot and the turgor poor. Mild nuchal rigidity, positive Kernig's, and positive Brudzinski's signs were present, and there was definite spasticity of all extremities.

Pertinent laboratory findings and therapy are illustrated in Fig. 2. The infant became afebrile on the seventh hospital day. On the fourteenth and fifteenth days he had an elevation of temperature due to an upper-respiratory infection which subsided without additional therapy. There were no apparent residua at the time of discharge on Jan. 27, 1950.

CASE 2.—R. B., a 14-month-old Negro male infant (Fig. 3), was admitted to the hospital on Dec. 26, 1949. This infant had been apparently well, except for a "cold" of seven days' duration, until Dec. 23, 1949, at which time he was thought to have fever, had refused to eat, and was disinclined to play. He remained drowsy for the next two days and was brought to the hospital. He had received aspirin and nose drops prior to admission. Physical examination revealed a lethargic infant who responded to stimulation. The anterior fontanel was small. The fronto-occipital circumference was 50.5 cm. There was severe pharyngitis and moderate bilateral catarrhal otitis media. Definite nuchal rigidity, positive Kernig's, and positive Brudzinski's signs were present. Pertinent laboratory findings and therapy are illustrated in Fig. 3. The infant became afebrile within six days with one subsequent elevation on the fifteenth and sixteenth hospital days. At this time a right purulent otitis media and acute pharyngitis were observed. A culture of the nasopharynx showed the presence of a mixture of gram-positive organisms. There were no apparent residua at the time of discharge on Jan. 30, 1950.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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 27 34
THERAPY
CHLOROMYCETIN ORAL 150 MG/KG/24 HRS.
RECTAL TEMP.
URI.
SPINAL FLUID
WBC 7400 83 5
% POLYS 99 40 0
SMEAR + -
CULTURE + -

Fig. 2.—R. M., a 6-month-old Mexican male infant weighing 5 kg., with *H. influenzae* meningitis.

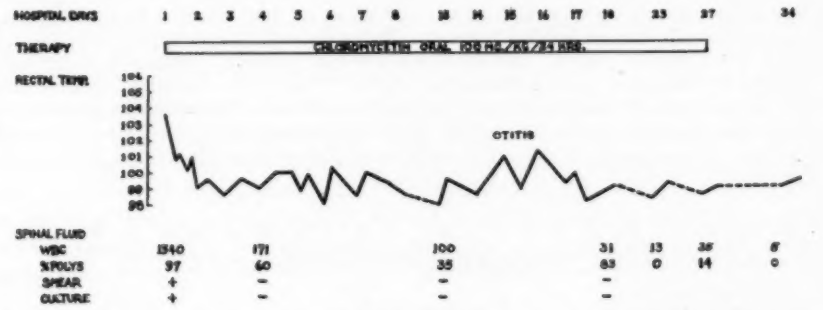
HOSPITAL DAYS
1 2 3 4 5 6 7 8 10 14 15 16 17 18 23 27 34
THERAPY
CHLOROMYCETIN ORAL 100 MG/KG/24 HRS.
RECTAL TEMP.
OTITIS
SPINAL FLUID
WBC 1340 171 100 31 13 35 5
% POLYS 97 60 35 63 0 14 0
SMEAR + - - -
CULTURE + - - -

Fig. 3.—R. B., a 14-month-old Negro male infant weighing 11 kg., with *H. influenzae* meningitis.

Case 3.—E. B., a 24-month-old Negro male infant (Fig. 4), was admitted to the hospital on Dec. 29, 1949. He was the older brother of R. B., who had been admitted three days previously with meningitis due to *H. influenzae*. This child had been perfectly well until ten days prior to admission when he developed an upper-respiratory infection. The night before admission he had fever and complained of pain in the lower extremities. On the morning of admission he was drowsy, had vomited, and had clonic movements of the lower extremities. Aspirin

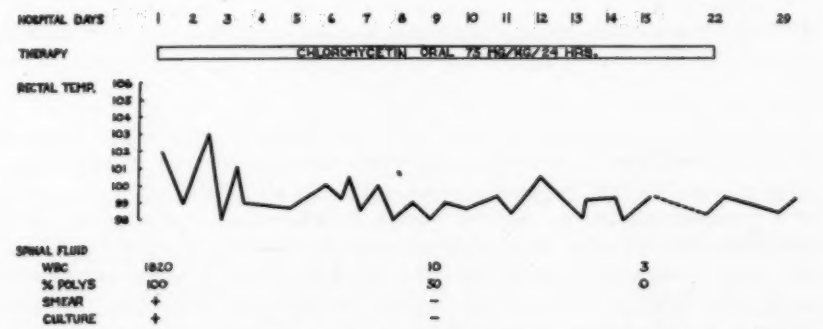
HOSPITAL DAYS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 22 29
THERAPY
CHLOROMYCETIN ORAL 75 MG/KG/24 HRS.
RECTAL TEMP.
SPINAL FLUID
WBC 1820 10 3
% POLYS 100 50 0
SMEAR + -
CULTURE + -

Fig. 4.—E. B., a 24-month-old Negro male infant weighing 17 kg., with type B *H. influenzae* meningitis.

was the only medication received by the patient prior to admission. Physical examination revealed an acutely ill child who was stuporous and responded slowly. The anterior fontanel was closed. The fronto-occipital circumference was 50.5 cm. The tonsils were large and covered with a purulent exudate. There was definite nuchal rigidity and positive Brudzinski's sign; Kernig's sign was not present. Pertinent laboratory findings, therapy, and hospital course are illustrated in Fig. 4. There were no apparent residua at the time of discharge on Jan. 30, 1950.

CASE 4.—K. S., a 13-month-old Negro male infant (Fig. 5), was admitted on Jan. 3, 1950. This infant was reported to have had a "cold" for three weeks prior to admission. On the afternoon of admission he began to "shake all over" and became stuporous, arousing only when his neck was manipulated. He had been treated at home with Mentholatum rubs, laxatives, and aspirin. Physical examination revealed a lethargic infant of good nutritional status who was acutely ill. The fronto-occipital circumference was 46 cm. A mild internal strabismus was present on the right. The pharynx was injected and mild bilateral catarrhal otitis media was present. There was moderate nuchal rigidity and positive Brudzinski's sign. Kernig's sign was not present. Pertinent laboratory findings and therapy are illustrated in Fig. 5. The infant was soon afebrile, but had an elevation of temperature on the eighteenth and nineteenth hospital days, which was thought to be the result of an upper-respiratory infection of viral etiology. There were no apparent residua at the time of discharge on Jan. 31, 1950.

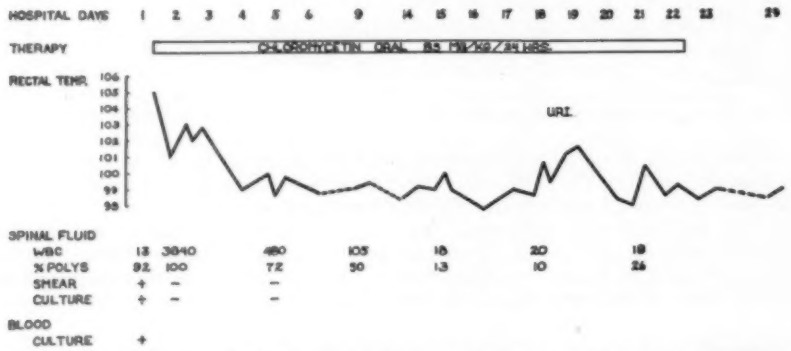

Fig. 5.—K. S., a 13-month-old Negro male infant weighing 14 kg., with type B *H. influenzae* meningitis.

COMMENT

The favorable response obtained with oral Chloromycetin in the treatment of a refractory case of influenzal meningitis prompted the use of oral Chloromycetin alone in four subsequent cases of this disease. The therapeutic results were good and consistent. Several aspects of these cases are of interest. While receiving what appeared to be adequate amounts of Chloromycetin for the control of the meningitis, three of the infants had elevations of temperature, which in all three instances were attributed to upper-respiratory infections. In Case 2 pharyngitis and purulent otitis media were noted. Bacterial culture of the nasopharynx revealed the presence of a mixture of gram-positive organisms. In Cases 1 and 4 there were no definite localizing signs, and the upper-respiratory

infection was presumably of viral etiology. With no therapy other than Chloromycetin the secondary upper-respiratory infection cleared in a few days.

Nevertheless, in view of the known symbiosis of staphylococci and *H. influenzae* and of such clinical experiences as these, in which upper-respiratory infections complicated the convalescence of patients with influenzal meningitis, the authors feel that other antibiotics and chemotherapeutic agents, particularly those effective against gram-positive organisms should supplement Chloromycetin in the management of this disease. It should be emphasized likewise that *H. influenzae* has been shown susceptible to other antibiotic and chemotherapeutic agents and that optimal management of severe infections caused by *H. influenzae* will probably require other therapeutic agents in combination with Chloromycetin.

Although previously reported,[10] the occurrence of influenzal meningitis in siblings is rare. Two of the cases reported here were in brothers, onset occurring in the two infants within three days of each other. The possibility of the occurrence of this disease in siblings should be kept in mind.

Rapid clinical improvement and parallel improvement in the spinal fluid findings were striking features in all these cases. No residua were noted in any of the infants at the time of discharge. The response of influenzal meningitis to this simplified therapeutic regimen was quite satisfactory. However, this is a preliminary report and subsequent clinical observation will be made in the outpatient department with special attention given to the possible development of sequelae.

SUMMARY

After successful treatment with Chloromycetin by oral route of one infant with meningitis due to *H. influenzae*, which was refractory to the usual therapeutic agents, four other infants with this disease were treated with Chloromycetin alone. The results were gratifying and encouraging, and to date recovery in all instances appears complete.

REFERENCES

1. Levinson, A.: Meningitis, in McQuarrie, I., Brennemann's Practice of Pediatrics, Hagerstown, Md., 1949, W. F. Prior Company, Inc., vol. 4, chap. 8, pp. 65 to 68.
2. Pittman, M.: Antibacterial Action of Several Sulfonamide Compounds on *Hemophilus Influenzae*, Type B, Pub. Health Rep. **57**: 1899, 1942.
3. Alexander, Hattie E.: Experimental Basis for Treatment of *Hemophilus Influenzae* Infections, Am. J. Dis. Child. **66**: 160, 1943.
4. Alexander, Hattie E.: Type B Anti-Influenzal Rabbit Serum for Therapeutic Purposes, Proc. Soc. Exper. Biol. & Med. **40**: 313, 1939.
5. Committee on Chemotherapeutic and Other Agents, National Research Council: Streptomycin in the Treatment of Infections: A Report of One Thousand Cases, J. A. M. A. **132**: 4, 1946.
6. Alexander, Hattie E., and Leidy, Grace: Influence of Streptomycin on Type B *Hemophilus Influenzae*, Science **104**: 101, 1946.
7. Crook, William G., Clanton, B. Reed, and Hodes, Horace L.: *Hemophilus Influenzae* Meningitis, Pediatrics **4**: 643, 1949.
8. Long, Perrin H., Chandler, Caroline A., Bliss, Eleanor A., Bryer, Morton, and Schoenback, Emanuel: The Use of Antibiotics, J. A. M. A. **141**: 315, 1949.
9. Ross, S., Burke, F. G., Rice, E. C., and Washington, J. A.: As quoted in *Chloromycetin*, Parke, Davis & Co., 1949.
10. Hertzog, A. J., Cameron, Isabell Logan, and Karlstrom, A. E.: Influenzal Meningitis in Brothers, J. A. M. A. **124**: 502, 1944.

REPORT OF A CASE OF INFLUENZAL MENINGITIS TREATED WITH POLYMYXIN B (AEROSPORIN)

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UNTIL comparatively recently, influenzal meningitis carried with it an almost 100 per cent fatality rate. With the introduction of sulfanilamide, the mortality rate decreased slightly and was reduced still further with sulfadiazine. The use of specific rabbit antiserum for *Hemophilus influenzae*, type B, introduced by Alexander in 1939, brought about a further improvement. But with the advent of streptomycin there was a much more marked drop in the mortality rate. Now there is a nearly 100 per cent recovery with the use of streptomycin alone or in combination with sulfadiazine and specific rabbit antiserum. But in severe cases, Alexander[2] states, there may be failures with the use of streptomycin due to the existence of resistance of some of the strains of the organisms. In a later report, Alexander[3] states, "In mild or moderately severe cases, either streptomycin alone or sulfadiazine in conjunction with specific rabbit antiserum, can be expected to cure 100 per cent of them. . . . Those patients with severe, chronic or uncontrolled meningitis should receive sulfadiazine, streptomycin, and specific rabbit antiserum simultaneously, as these three agents exert their destructive influence through three different mechanisms. This is especially important in young infants."

In a recent article by Kagan,[4] he reports the successful treatment of a 13-month-old infant with a new antibiotic, Polymyxin B (aerosporin). This infant had been treated with streptomycin and sulfadiazine for several weeks without improvement and had not been given specific rabbit antiserum until late in the course of the disease. Because the child was desperately ill, a new antibiotic, Polymyxin B, was begun and the patient recovered.

Polymyxin A was first reported in England in 1947 by Ainsworth, Brown, and Brownlee.[5] It was isolated from soil and called aerosporin, as the organism from which it is derived is *Bacillus aerosporus*, which may be *Bacillus polymyxa*. They state that it is selective in its action against gram-negative organisms. It is bactericidal in action and cultural methods have failed to produce resistant strains. It is relatively stable, readily produced, and is of high intrinsic potency. Weight for weight, it has the same order of chemotherapeutical activity against gram-negative organisms as has penicillin against gram-positive.

About the same time Stansly, Shepherd, and White,[6] working independently in this country, reported that an organism had been isolated from soil which produced on agar plates a wide zone of inhibition of the gram-negative pathogen, *Salmonella schottmülleri*. The antibiotic-producing organism was identified as *B. polymyxa*. They state that polymyxin is specific for gram-negative bacteria. It is therapeutically active in experimental infections in mice and is relatively nontoxic. From a variety of sensitive species, strains resistant to polymyxin were not obtained under conditions which readily yield strains completely resistant to streptomycin.

In 1948, Brownlee and Bushby[7] report further on Polymyxin A, the form of the antibiotic produced in England. They say, "The high activity of aerosporin in the test tube against strains of *H. influenzae* and its equal efficiency with streptomycin in the treatment of intracerebral infections of mice, indicates that aerosporin may be at least as effective as streptomycin in *H. influenzae* meningitis in man. It is well tolerated intrathecally in rabbits and a therapeutic concentration in the cerebrospinal fluid may be maintained for twenty-four hours after a single dose. . . . Its action is restricted to several gram-negative pathogens against which it is from ten to many hundreds times more active than streptomycin. It is not absorbed from the gut. When given parenterally it disappears from the blood stream quickly, hence four-hourly maintenance doses are necessary. It is more acutely toxic than streptomycin, but in terms of intrinsic antibacterial efficiency their therapeutic indices are of the same order. It is nonhemolytic. Aerosporin concentrates are more or less contaminated with an antidiuretic principle and a substance which damages the renal tubules. Purified material is free from the second factor and the first has not been shown to act in man."

Schoenbach, Bryer, and Bliss[8] report the use of polymyxin in total daily doses of up to 5 mg. per kilogram of body weight, given in a special buffer solution (pH 7.4) at intervals of three hours. They say, "Its acute toxicity in experimental animals is considerably greater than that of penicillin or streptomycin. After intramuscular injection it promptly enters the blood stream but does not pass the blood-brain barrier. It is excreted slowly in the urine. In certain experimental infections produced by the inoculation of gram-negative organisms in mice, polymyxin appears to be definitely more effective than streptomycin."

Because of the favorable report by Kagan on the use of Polymyxin B in a case of severe influenzal meningitis in an infant, it was decided to try it in a case of influenzal meningitis in a 3-year-old child recently admitted to Mountainside Hospital, Montclair, N. J. This was apparently also a severe case with a septic type of temperature curve reaching as high as 104.6° F. and the spinal fluid sugar at zero. There was a heavy growth of *H. influenzae*, type B in the spinal fluid and many organisms were seen in the direct smear. In the thirty-six hours which elapsed before the Polymyxin B* could be obtained, penicillin, sulfadiazine, and streptomycin were all used. But when the Polymyxin B was begun, all other treatment was discontinued except that 100 mg. of specific rabbit antiserum was given. Polymyxin B was used for eleven days with four doses given intrathecally. The temperature gradually returned to normal and the child recovered.

CASE REPORT

P. T., a Negro female child 3½ years old, was admitted to the hospital in the middle of the night, sent in by her family doctor with a diagnosis of pneumonia. She gave a history of having been ill at home for four days with an upper-respiratory infection and a cough. When she failed to improve, she was referred to the hospital. At the time of admission her temperature was 102° F.

*The Polymyxin B was supplied by Burroughs Wellcome & Co. (U.S.A.), Inc.

and she was lethargic. Her pupils reacted sluggishly but were equal. Her ears were normal and her throat was injected. Her neck was almost rigid; the abdominal reflexes were absent; the knee jerks were diminished; the Kernig's and Brudzinski's signs were both present. The lungs showed signs of consolidation in the right base posteriorly and there were scattered moist râles throughout.

A lumbar puncture, done the next morning, showed colorless, cloudy (ground glass) fluid under slightly increased pressure. The cell count was 500 white blood cells per cubic millimeter, 35 per cent polymorphonuclears, 65 per cent lymphocytes; glucose was 3 mg. per 100 c.c. and protein 98 mg. per 100 c.c. The smear showed short gram-negative bacilli. The culture yielded a heavy growth of *H. influenzae,* type B. At the time of the spinal puncture, she was given 25 mg. of streptomycin intrathecally. The other laboratory findings on admission were as follows: hemoglobin 9.5 Gm. per 100 c.c., red blood count 3.4 million per cubic millimeter, white blood count 15.8 thousand per cubic millimeter with 77 per cent polymorphonuclear cells, 22 per cent lymphocytes, 1 per cent monocytes; sedimentation rate 117. A chest x-ray showed hazy densities scattered throughout both lung fields and moderate cardiac enlargement. The tuberculin patch test was negative. Two blood cultures taken the second and third days after admission were sterile. She was started on penicillin 30,000 units every three hours, streptomycin 125 mg. intramuscularly every four hours, and sulfadiazine 1.0 Gm. the first dose, then 0.5 Gm. every four hours.

Another spinal puncture was done the next day. The pressure was 220 mm. of water. The fluid was still slightly cloudy. The cell count was 736 white blood cells per cubic millimeter with 66 per cent lymphocytes. The glucose was zero. She was given 50 mg. of streptomycin intrathecally. The spinal fluid culture was still positive for *H. influenzae,* type B. The child's condition remained about the same with the temperature going up to 104.6° F. She was lethargic and had a completely rigid neck. The chest signs were the same as on admission.

On the evening of the second day the Polymyxin B was received and all other treatment was discontinued. Polymyxin B in normal saline 10 mg. (100,000 units) was given intramuscularly every four hours. A third lumbar puncture was done and 1 mg. (10,000 units) was given intrathecally.

The following day 35 mg. (35,000 units) of Polymyxin B were given intrathecally. As this lumbar puncture was slightly bloody, it was of no value for determining cell count or protein, but the culture was sterile. On this same day she was given 100 mg. of specific rabbit antiserum. The following day the patient's serum showed capsular swelling with *H. influenzae* isolated from the spinal fluid.

The following day, the third from the beginning of this new therapy, 35 mg. (35,000 units) of Polymyxin B were again given intrathecally. The spinal fluid was very slightly cloudy, the cell count was 300 white blood count with 84 per cent lymphocytes, and the glucose was 51 mg. per 100 c.c.; the protein was 98 mg. per 100 c.c.; the chlorides 677. There was no growth on culture. The child's condition remained much the same with a high septic type of temperature and a very stiff neck. As her hemoglobin had dropped to 8 Gm., she was given two transfusions of whole blood, 250 c.c. each, twenty-four hours apart. Following this she became more alert and began to eat better.

The fourth day from the beginning of therapy, 35 mg. (35,000 units) of Polymyxin B were given intrathecally for the third and last time. This lumbar puncture was again slightly bloody and so unfit for cell count. The patient was showing gradual improvement. Her temperature range was less, she was turning over in bed, was eating better, and was more alert. Her blood count had improved. Two days after the transfusions, the hemoglobin was 12 Gm. per 100 c.c.; red blood count 4.1 million per cubic millimeter; white blood count 18.9 thousand per cubic millimeter with 83 per cent polymorphonuclears. Daily urine

analyses had shown no albumin but an occasional hyalin cast. Whether this was due to the treatment or to the infection, it is not possible to say.

Four days after the last intrathecal treatment with Polymyxin B, the lumbar puncture showed clear fluid, white blood count 154, mostly lymphocytes; protein 96 mg. per 100 c.c.; sugar 56 mg. per 100 c.c.; chlorides 677 mg. per 100 c.c.

Three days after this lumbar puncture, another one was done which showed white blood count 72 with 92 per cent lymphocytes; sugar 48 mg. per 100 c.c.; protein 48 mg. per 100 c.c. At this point the intramuscular treatment with Polymyxin B was discontinued; 10 mg. (10,000 units) had been given continuously every four hours for ten days. The high spiking temperature began to come down after eight days. A final lumbar puncture, done ten days after treatment had been stopped, showed white blood count down to 45 and sugar 68 mg. per 100 c.c.

Because she continued to run a low-grade fever, between 100° and 100.6° F. she was given dihydrostreptomycin 100 mg. intramuscularly every six hours for four days. A later communication from Burroughs Wellcome & Co. has suggested that this low-grade fever may be a form of toxicity from the Polymyxin B. No other toxic manifestations were noted.

The child had improved greatly; her neck was no longer stiff; she was talking and playful and was eating well. Her lung signs had nearly cleared. A few days before she was allowed out of bed, a coarse tremor of the hands was noted, but this soon cleared. When she was allowed to get up and begin walking, a definite unsteadiness of gait was observed with a positive Romberg sign. This unsteadiness decreased but was still present on her discharge from the hospital. Except for this she seemed to be a normal child when she left the hospital twenty-eight days after admission. She had gained 4 pounds in weight and was eating well.

A week after her discharge she was seen in the clinic. She was still slightly unsteady but not as much as at the time she left the hospital. Whether this was due to her intrathecal treatment with Polymyxin B or streptomycin or to her illness, no one can tell. Seven weeks after discharge from the hospital this unsteadiness seemed to have disappeared completely. She could walk and run like any child her age and her mother said she seemed to be in as good condition as before her illness.

SUMMARY

A 3-year-old Negro child with severe influenzal meningitis was treated with a new antibiotic, Polymyxin B (aerosporin), which was given four times intrathecally and for eleven days intramuscularly with apparent complete recovery. Previous to this treatment, for thirty-six hours she had been given streptomycin, penicillin, and sulfadiazine. No toxic effects were noted except a moderate unsteadiness in gait and this disappeared completely in a few weeks.

REFERENCES

1. Alexander, Hattie E.: Type B Anti-Influenzal Rabbit Serum for Therapeutic Purposes, Proc. Soc. Exper. Biol. & Med. **40**: 313, 1939.
2. Alexander, Hattie E.: Streptomycin in Pediatrics, J. PEDIAT. **29**: 192, 1947.
3. Alexander, Hattie E., and Leidy, Grace: Present Status of Treatment of Influenzal Meningitis, Am. J. Med. **2**: 457, 1947.
4. Kagan, B. M.: Influenzal Meningitis; Recovery of a Case of Four Weeks' Duration With the Use of a New Drug, Polymyxin B (aerosporin), Pediatrics **4**: 323, 1949.
5. Ainsworth, G. C., Brown, A. M., and Brownlee, G.: Aerosporin, Antibiotic Produced by Bacillus Aerosporus Greer, Nature **160**: 263, 1947.
6. Stansly, P. G., Shepherd, R. G., and White, H. J.: Polymyxin: New Chemotherapeutic Agent, Bull. Johns Hopkins Hosp. **81**: 43, 1947.
7. Brownlee, G., and Bushby, S. R. M.: Chemotherapy and Pharmacology of Aerosporin, Lancet **1**: 127, 1948.
8. Schoenbach, E. B., Bryer, M. S., Bliss, E. A., and Long, P. H.: Polymyxin, J. A. M. A. **136**: 1096, 1948.

COARCTATION OF THE AORTA IN EARLY INFANCY

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COARCTATION of the aorta is one of the congenital cardiovascular anomalies in which a diagnosis can be made with certainty during life. In spite of a definite clinical picture, the diagnosis is rarely made in infants and children.[1] Twenty years ago Blackford[2] in a thorough review of the literature found that the clinical diagnosis of coaretation in children had been reported in only four cases. In the same review he stated that coaretation in all age groups had been definitely diagnosed clinically in seventy-eight cases and corroborated by post-mortem examination only twenty-one times.

The occurrence of coaretation of the aorta is not rare. Blackford[2] in 1928 estimated that coaretation of the aorta was found once in every 1,550 autopsies. Evans[3] in 1932 stated that it occurred once in every 1,000 autopsies. Abbott[4] in her series of 1,000 cases of congenital heart disease records coaretation of the aorta as occurring 178 times; 105 of these or 60 per cent were of the adult type. Perlman[5] in a study of inductees for the army found it occurring once in 10,000 men.

The comprehensive and interesting contributions to the subject of coaretation of the aorta by Abbott[6] (1928), Blackford[2] (1928), King[7] (1926), and Lewis[8] (1932), and others stimulated the medical profession to be on the alert for this congenital anomaly. As a result, in the decade between 1930 and 1940, more cases were diagnosed clinically than in the entire history of coaretation since 1791[9] when the first case was reported. Eisenberg[10] stated that between 1928 and 1938 eleven authentic cases of coaretation were reported in children. He reported three more, the youngest of which was 2½ years old. However, for the same period forty cases were recognized in adults. Since most students of the subject now believe that every case of coaretation in adults is present in the newborn infant, the diagnosis could be made more often in children. Eisenberg[10] advised that palpation for femoral pulsations in the routine examination of children would increase the number of cases recognized clinically. In 1941, Blumenthal and Davis[11] reported a case of coaretation diagnosed in a child 20 months old on the basis of (1) hypertention in the upper extremities, (2) failure to obtain a blood pressure reading in the lower extremities, (3) absence of femoral pulsations, and (4) systolic murmur in the interscapular area. These authors were among the first to report the use of intravenous radiopaque substances to visualize the coaretation. Wilson in 1940[12] reported the youngest case of coaretation in an infant 18 months old. The basis for the diagnosis was (1) elevated blood pressure in the upper extremities, (2) lower blood pressure in the lower extremities, and (3) a bruit heard over both scapulae.

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Rhodes and Durbin[13] in 1942 stated that the total number of cases of coaretation diagnosed clinically in children reported in the entire literature had increased to forty-seven. In 1942, Schwartz and Greene[14] reported for the first time in a child an unusual case of coaretation in which the blood pressure in the right arm was elevated and was absent in the left arm and lower extremities. The coaretation in such cases occurs proximal to or at the origin of the left subclavian artery.

In spite of the increasing frequency with which the clinical diagnosis of coaretation has been made in children, a careful survey of the literature has failed to reveal a single case report of coaretation diagnosed in the newborn or young infant corroborated by autopsy finding.[3] Gross[15] in 1949 reported observing six babies in the first year of life with aortic obstruction.

Abbott[6] and Blackford[2] who contributed a great deal to the subject of coaretation in adults, unfortunately, did not stimulate the study in newborns and infants. Abbott[6] stated that coaretation in infants is of little clinical imporance except insofar as it may complicate other grave anomalies. Blackford[2] concluded that the clinical diagnosis in such cases (infants and young children) is of little or no actual importance because coaretation of the infantile type is rapidly fatal or, if of the adult type, is hardly a factor in causing death. It will be the purpose of this presentation to show that coaretation in infants is clinically important. Many of these cases can be diagnosed during life and are not associated with other serious congenital anomalies. With the recent advances in great blood vessel surgery, it may be possible to operate on and save a few of these infants who would ordinarily have no chance to survive.

In 1945, both Craaford[17] and Gross[18] independently reported a significant achievement in great blood vessel surgery. They successfully operated on patients with coaretation of the aorta. The operation consisted in excising the constricted portion of the aorta and anastomosing the two ends. In November, 1946, Potts, Smith, and Gibson[19] reported the successful anastomosis of the aorta to the pulmonary artery in a child. They used a special aortic clamp which permits part of the blood to pass through the aorta during the operation. Clagett[20] in 1947 reported the first successful anastomosis of the left subclavian artery to the aorta by-passing the coaretation in a human subject. Gross[21] in 1948 reported the successful use of human arterial grafts in the treatment of coaretation of the aorta. These achievements of modern surgery and their possibilities make the diagnosis of coaretation in the newborn and young infant a matter of vital importance as will be pointed out later.

Coaretation is a narrowing of the arch of the aorta usually below the origin of the left common carotid artery. The constriction occurs most frequently at the level of the mouth of the ductus arteriosus or at the place of attachment of the obliterated ligamentum arteriosum. The narrowing may partly or completely occlude the lumen; it may be diffuse or sharp as if a string were tied around the vessel.

Coaretation is commonly classified into two types. The *infantile type* refers to a narrowing of the aortic arch proximal to the mouth of the ductus arteriosus. The *adult type* is a narrowing of the arch at or just distal to the mouth of the ductus. The infantile type is usually associated with a patent ductus, a more diffuse type of narrowing, and early death. The adult type is usually associated with a sharp constriction, a closed ductus, an extensive collateral circulation, and much longer life. It must be emphasized that there are exceptions to each of these associated characteristics. For instance, Abbott[6] reported nineteen of her 200 subjects with adult coaretation as having a patent ductus arteriosus. We have noted in our series seven cases of infantile coaretation with a sharp constriction of the aorta. Moreover, we have also observed four cases with both the adult and infantile types of coaretation in the same patient. Reifenstein and associates[22] cite thirteen such cases in their series; Benkwitz and Hunter[23] have also reported this latter finding.

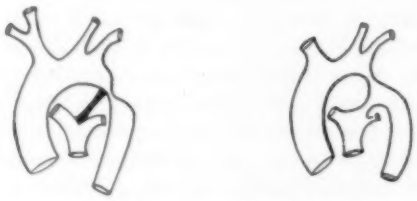

Fig. 1.—Diagrammatic representation of infantile and adult types of coaretation of the aorta.

The classification of the infantile and adult types is most useful from an anatomic and clinical point of view. Unfortunately, the terms are misleading and have led many to assume that all cases of coaretation occurring in infants are necessarily of the infantile type. This assumption is incorrect as may be demonstrated by autopsy reports describing the adult type in newborns and infants.[2, 6, 23, 24] Two more such cases will be presented in this report. Moreover, to add to the confusion of terms, frequently the infantile type is found in adults. Abbott[6] reports eight such cases in a survey of 200 cases of adult coaretation. For convenience she classifies these cases as belonging to the adult type. Johnson and Kirby[25] report finding on surgical exploration three cases of the infantile type in patients 13, 17, and 20 years old, respectively. Adams and associates[26] also report three cases of infantile coaretation in adults who came to surgery.

Consequently, Blumenthal and Davis[11] proposed the terms "compensating" for the adult type and "noncompensating" for the infantile type on the basis of the presence or absence of a collateral circulation. However, a number of cases of the adult type have been described without collateral circulation.[2, 6, 27] More accurate anatomical terms would be "preductal" and "postductal" type coaretation, preductal for the infantile type and postductal for the adult type of coaretation.

Bonnett,[28] who first proposed this classification of adult and infantile types in 1891, considered the infantile type a result of fetal maldevelopment. The adult type was believed to be acquired after birth and intimately associated with the closing of the ductus. The same process caused the closing of both vessels. It was believed that some of the muscle fibers in the ductus were prolonged into the aorta, and the constriction of the ductus constricted the aorta. This idea cannot be maintained because no such common muscle or elastic tissue has been found. Moreover, many cases of the adult type are found with a patent ductus. At present the most widely accepted theory of pathogenesis maintains that both the infantile and adult types of coaretation arise from a defect in the development of the fourth aortic arch and its junction with the dorsal aorta and the sixth aortic arch (precursor of the ductus arteriosus).[29] This takes place in the second month of fetal life. From a fundamental consideration of this theory we must conclude that both the infantile and adult types should be found in fetuses and newborn infants. In other words, every case of coaretation found in older children and adults existed in utero and in the newborn infant. Some have criticized this theory[28, 3] on the ground that although fetuses have been described with the infantile type, no fetus was found with an adult type of coaretation. We wish to cite Cases 4 and 8 described by Ingham[30] in 1939, as examples of the adult type of coaretation occurring in fetuses 6 and 5½ months of age respectively.

There is an amazing difference in the clinical course and prognosis between the two types. The patient with the infantile type usually succumbs soon after birth or within the first few months of life. The infant with the adult type as a rule survives. Seveny-five per cent reached the age of 20 in Abbott's[6] series of 200. In the review by Reifenstein and associates,[22] 104 patients reached the average age of 35. Many of them have been known to engage in heavy manual work or arduous athletics. Ballantyne[31] offers a logical explanation for this great difference.

In the adult type the constriction is opposite to or distal to the entrance of the ductus arteriosus. Consequently, there is interference with the free flow of blood into the descending aorta both by way of the aorta and by the way of the ductus arteriosus. It is imperative that an adequate collateral circulation be established in early embryonal life if the fetus is to survive even in utero, since survival is impossible without a sufficient flow of blood into the descending aorta. Owing to the forced establishment of a collateral circulation in fetal life, the infant is much better equipped to meet successfully the strains put on him in early and later postnatal life.

In cases of the infantile type with the constriction proximal to the entrance of the ductus, the flow of blood through the ductus remains unimpaired. An adequate circulation can be carried on in the fetus by the transfer of the extra work to the right ventricle without the establishment of a collateral circulation. In other words, there is no stimulus to the establishment of a collateral circulation until after birth. At this time the infant is ill-fitted, often incompetent, to establish a circulation of the extrauterine type adequate to meet the strains of postnatal life.

The collateral circulation[6] which develops in most cases of adult coarctation is carried on between branches of the subclavian artery and the aorta below the point of constriction. The superior intercostals anastomose with the aortic intercostals. Branches of the subscapular arteries anastomose with the upper aortic intercostal arteries and the internal mammaries with inferior epigastrics.

SERIES OF CASES

Twenty-one autopsied cases of coaretation of the aorta in infants are presented in Table I. Six in this series were found between 1938 through 1946, and sixteen were diagnosed from 1947 through 1949.

The cases are arranged according to the anatomic findings on autopsy. One subject was not autopsied.* The first two cases are examples of adult coaretation. Cases 3 through 7 are a combined type of adult and infantile coaretation. Cases 8 through 21 are the infantile type of coaretation with either a sharp or diffuse constriction of the aorta.

CLINICAL FEATURES

Sex.—There were thirteen male subjects and nine females in this series. This distribution is at variance with the reported findings in cases of "adult coaretation" where the males greatly predominate. Thus Abbott[6] in her series of 200 cases gives a ratio of 4 to 1; Reifenstein and associates[22] find a ratio of 5 to 1 in their series of 104 cases.

Condition at Birth.—Seventeen infants appeared to be normal at birth. Of the remaining five, two had persistent cyanosis. In both cases there were serious congenital abnormalities of the heart and great blood vessels (Cases 15 and 20). Two others had intermittent cyanosis since birth and at autopsy were found to have large septal defects (Cases 16 and 21). One infant had severe choking spells due to hypoplasia of the mandible with obstruction of the pharynx by the tongue. In three infants considered normal at birth the parents noted some abnormality of breathing or color. These histories were too vague to be considered as a definite abnormality at birth (Cases 1, 3, and 4).

Age at Onset of Symptoms and Death.—Seventeen infants developed signs or symptoms of cardiorespiratory distress during the first fourteen days of life; eighteen died during the first eight weeks of life. Of the remaining four, one died at 67 days; two died at 4 months, and one died at 20 months of age.

Hypertension in Upper Extremities.—Blood pressure studies were recorded in seventeen patients using the 2.5 cm. cuff. Clement Smith[33] in his review of normal blood pressure of newborn infants concludes that the average blood pressure in the newborn infant is 80 systolic and 46 diastolic. The sytolic usually reaches 95 to 100 on the fourteenth day. There is a further change of 2.5 to 5 mm. Hg during the first year. The diastolic rises a little less than 20 mm. Hg during the first two weeks. We used these criteria as the upper level of normal in young infants.

In fourteen of seventeen cases in which blood pressures are recorded, there was an elevation of systolic blood pressure in both upper extremities.

*This case was not included in Table I.

In four of these cases diastolic pressure in the upper extremities could not be obtained. There was an elevation of both diastolic and systolic pressure in twelve cases.

The systolic blood pressure ranged from 100 to 190. The diastolic pressure ranged from 70 to 130. The three infants whose systolic blood pressures were considered normal had recordings of 100/80, 100/?, and 105/? respectively. The first one of the infants had a dextroposition of the aorta, interventricular septal defect, and patent foramen ovale. The second infant had a mild coarctation which was constricted to less than 60 per cent of the cross-sectional area of the aortic ring and a widely patent ductus opening distal to the coarctation. The third infant had an atresia of the mitral valve, hypoplasia of the left ventricle, interventricular septal defect, and patent foramen ovale. We observed one infant with coarctation and severe cardiac failure who was seen initially with a blood pressure of 100/60; twenty-four hours later the infant was much improved, and the same observer found a blood pressure of 140/90.

Brachial and Radial Pulses.—The radial and brachial pulsations were full and very strong in every case whenever noted.

Femoral Pulse.—Palpation of the femoral pulses was noted in twenty cases. In ten cases the femoral pulses were absent or barely palpable. In ten cases femoral pulses were definitely palpable. In nine of these instances, the ductus was widely patent. In one case (Case 18) where the ductus was small, the coarcted segment was mildly constricted; constriction was 11 mm. in circumference as compared with a circumference of 17 mm. for the aortic ring. It is evident from these findings that the diagnosis of coarctation of the aorta cannot be excluded solely because femoral pulsations are present. If the femoral pulsations are very feeble or cannot be felt, there is a strong likelihood that the ductus arteriosus is small or opens into the aorta at or proximal to the site of coarctation.

Blood Pressure in Lower Extremities.—In fourteen of the seventeen infants no blood pressure could be obtained in the lower extremities. In the one instance (Case 18), a systolic pressure of 90 was obtained in the legs with a systolic reading of 100 in the upper extremities. The infant had a mild coarctation, 9 mm. circumference, and a very widely patent ductus, 11 mm. circumference.

Murmurs.—A systolic precordial murmur was heard in fifteen cases. The murmur was usually not audible over the back. An outstanding feature of the murmur was its inconstancy. Examination on the same day would reveal a murmur at one time, and several hours later it could not be heard. Several of the infants were known to have been examined by physicians soon after birth at which time no cardiac murmur was detected.

Cardiorespiratory Distress.—At the time of first examination twenty infants had cardiorespiratory distress characterized by rapid, grunting, labored respirations with supra- and infraclavicular retractions. Unusually rapid respirations were noticed by parents in three cases from birth. Medium and fine râles were usually present in one or both lung fields. Gallop rhythm was recorded in ten cases.

TABLE I. CLINICAL AND PATHOLOGIC FINDINGS IN TWENTY-TWO CASES OF COARCTATION OF THE AORTA

CASE NO. AND SEX	AGE AT ONSET OF SYMPTOMS	AGE AT DEATH	CONDITION AT BIRTH	DIAGNOSIS MADE CLINICALLY?	BLOOD PRESSURE ARMS*	FEMORAL PULSATIONS	CLINICAL SIGNS OF HEART FAILURE					ASSOCIATED ILLNESSES
							RESPIRATORY DISTRESS	EDEMA	CYANOSIS	ENLARGED LIVER (NO. FINGERS BELOW COSTAL MARGIN)	MURMURS AND HEART SOUNDS GALLOP RHYTHM	
1. T. F. N. male	11 da.	22 da.	Normal	Yes	160/88 R 162/85 L	Very weak; no B.P. obtained; dorsalis pedis not felt	Severe; no râles in lungs	Edema of face on 16th day	Ashen-gray color 3 days prior to death	4 fingers	None; heart sounds of good quality	Hemorrhagic disease of newborn
2. C. D. S. male	123 da.	125 da.	Difficult breathing, no cyanosis	No	Not done	Not noted	Moderate; crepitant râles in both lungs	None	Marked cyanosis on admission; died same day	2 fingers	Murmur noted 2 da. prior to death, not on admission	Bilateral otitis media; pneumonia; upper-respiratory infection
3. S. R. female	4 wk.	6 wk.	Normal	Yes	150/100 R 130/90 L	Barely palpable; no B.P. could be obtained	Severe	Hands and feet to elbows and knees; some on face	Gray ashen appearance; cyanosis of feet, legs, hands, and forearms	1 finger	Systolic over apex; systolic and diastolic over pulmonic area not heard at first; heart sounds of good quality	Cold 3 weeks with cough and hoarseness
4. W. T. K. male	First 2 wk.	30 da.	Pallor and rapid respiration	Yes	110/60 on admission 24 hr. later 140/90 R 160/190 L 100	Faint; no B.P. obtained in legs	Severe; many moist râles in both lung bases	Legs, thighs, skin, and face	Mottled cyanosis face and skin	4 fingers	Not heard on admission; loud systolic later; heart sounds of poor quality; gallop rhythm	Pneumonia? Subarachnoid hemorrhage

TABLE I—CONT'D

CASE NO. AND SEX	TYPE OF COARCTATION	PATENCY OF DUCTUS	DEGREE OF AORTIC CONSTRICTION	SIZE OF HEART	RIGHT VENTRICLE THICKNESS (CM.)	LEFT VENTRICLE THICKNESS (CM.)	ASSOCIATED CONGENITAL CARDIOVASCULAR ANOMALIES	MISCELLANEOUS X-RAY, ECG, ANGIOCARDIOGRAPHY, AND PLETHYSMOGRAPHY	DIAGRAM
1. T. F. N. male	Adult	Patent	Not given; 0.3 cm. in length	Enlarged at autopsy, mainly right auricle and ventricle	0.6	0.6	Bicuspid aortic valve	On fluoroscopy, heart enlarged to right and left; heart size receded on 17th day, then dilated again	
2. C. D. S. male	Adult	Closed	Severe; 0.3 cm. in diameter; circumference of ascending aorta 3.2 cm.	92 grams; lower border beyond anterior axillary line	0.9	1.4	Bicuspid aortic valve; left A-V valve tricuspid; right A-V valve bicuspid	Heart sounds weak and rapid; died on day of admission	
3. S. R. female	Adult and infantile	Slight; 0.15 cm. in diameter	Severe; 0.15 cm. in diameter	Enlarged; P.M.I.† in left anterior axillary line	0.75	0.9	Moderate hypoplasia of the aorta; aorta starts narrowing distal to common carotid	X-ray: heart enlarged both to right and left; ECG: right axis deviation, inverted T in Lead I	
4. W. T. K. male	Adult and infantile	Slight; .25 cm. circumference	Severe; 0.1 cm. in diameter; practically entirely occluded	Enlarged; wt. 55 Gm.; diameter of chest 9 cm.; diameter of heart 7.3 cm.	0.7	0.8	Aorta starts narrowing distal to right innominate artery; constricts sharply at junction with ductus	ECG: Right axis deviation; $R_1R_2R_3$ splintered Fluoroscopy: Heart greatly enlarged to right and left	

TABLE I—CONT'D

CASE NO. AND SEX	AGE AT ONSET OF SYMPTOMS	AGE AT DEATH	CONDITION AT BIRTH	DIAGNOSIS MADE CLINICALLY?	BLOOD PRESSURE ARMS*	FEMORAL PULSATIONS	CLINICAL SIGNS OF HEART FAILURE					ASSOCIATED ILLNESSES
							RESPIRATORY DISTRESS	EDEMA	CYANOSIS	ENLARGED LIVER (NO. FINGERS BELOW COSTAL MARGIN)	MURMURS AND HEART SOUNDS GALLOP RHYTHM	
5. S. D. R. male	51 da.	52 da.	Normal	Yes	110/85 L 118/90 R	No pulse; B.P. not obtained	Severe; many fine râles over both lungs	Legs 1+	Dusky color	1.5 fingers	Systolic over apex; sounds of poor quality; gallop rhythm	Bronchopneumonia; thrush
6. M. M. male	10 da.	35 da.	Normal	Yes	At first not obtained; pulse feeble 180/130 R 170/100 L	Faint; no B.P. obtainable	Severe; few fine râles in both lung fields	None; some facial	Pallid; cyanosis	4 fingers	Inconstant systolic murmur over precordium; gallop rhythm	Mild pustular eruption
7. B. S. W. female	9th da.	28 da.	Normal	Yes	130/100 R 130/90 L	Present; no B.P. obtainable	Marked; no râles heard	Pitting edema of feet; slight peripheral edema	Grayish duskiness	4 fingers	Systolic over precordium; poor quality of heart sounds; gallop rhythm	Upper respiratory infection; sepsis(?)

TABLE I—CONT'D

CASE NO. AND SEX	TYPE OF COARCTATION	PATENCY OF DUCTUS	DEGREE OF AORTIC CONSTRICTION	SIZE OF HEART	RIGHT VENTRICLE THICKNESS (CM.)	LEFT VENTRICLE THICKNESS (CM.)	ASSOCIATED CONGENITAL CARDIOVASCULAR ANOMALIES	MISCELLANEOUS X-RAY, ECG, ANGIOCARDIOGRAPHY, AND PLETHYSMOGRAPHY	DIAGRAM
5. S. D. R. male	Adult and infantile	Slight patency	Mild; 1.1 cm. in circumference; ascending aorta 1.8 cm. in circumference	Greatly enlarged to right and left, especially to right; left border touches anterior chest wall (fluoroscopy)	1.2	0.8	Small interventricular septal defect; hypoplasia of right and left anterior cusps of aortic wall		
6. M. M. male	Adult and infantile	0.2 cm. in diameter	Complete closure; diffuse narrowing from left common carotid to point 3 mm. distal to ductus	20 grams† enlarged; apex at anterior axillary line	0.5	0.6	Bicuspid aortic valve; patent foramen ovale; hypoplasia of renal arteries	ECG: right axis deviation; T_2 flat, T_3 inverted, ST_2 depressed, ST_3 coved Fluoroscopy: heart enlarged to right and left Plethysmographic studies done; infant operated upon; narrowed and constricted portion of aorta removed; arterial graft anastomosed (21) mm. long. Infant died 20 minutes postoperatively	
7. B. S. W. female	Combined infantile and adult	Wide; 1.2 cm. in circumference; 0.8 cm. long	Severe and diffuse; 0.6 cm. in circumference; ascending aorta 2.0 cm. in circumference; descending aorta 1.5 cm. in circumference	60 grams	0.6	0.5	1. Patent foramen ovale 2. Interventricular septal defect (small)	ECG: right axis deviation Fluoroscopy: heart markedly enlarged to right and left	

TABLE I—CONT'D

CASE NO. AND SEX	AGE AT ONSET OF SYMPTOMS	AGE AT DEATH	CONDITION AT BIRTH	DIAGNOSIS MADE CLINICALLY?	BLOOD PRESSURE ARMS*	FEMORAL PULSATIONS	CLINICAL SIGNS OF HEART FAILURE					ASSOCIATED ILLNESSES
							RESPIRATORY DISTRESS	EDEMA	CYANOSIS	ENLARGED LIVER (NO. FINGERS BELOW COSTAL MARGIN)	MURMURS AND HEART SOUNDS GALLOP RHYTHM	
8. M. H. female	16 mo.	20 mo.	Normal	Yes	180/100 R 175/105 L	None; no B.P. obtained	Yes; severe	Hands, face, and legs		2 fingers	Heard on 2nd day of admission; sounds of poor quality; gallop rhythm	Bronchopneumonia; aspiration of fatty material
9. M. B. female	5 da.	23 da.	Normal	No	140/70	Good	Severe; no râles	On 14th day, noted on hands and feet	Peculiar gray color on 4th day; cyanosis 1 day prior to death	2 fingers; varied	Faint murmur on 5th day; rough systolic murmur on 7th day over precordium	Hemorrhagic disease of the newborn; diarrhea; upper-respiratory infection; bronchopneumonia; acute laryngo-bronchitis
10. R. D. male	5 da. Birth weight 11 lb.	49 da.	Normal	No	Not determined	Good	Severe; fine râles in both lung fields	On 24th day on lower extremities	5th day; cyanosis disappeared with treatment on 19th day metallic tinge to cyanosis	5-6 fingers; receded with treatment, then enlargement recurred	Systolic over 2nd left intercostal space, then heard over precordium; not constant; heart sounds of poor quality; gallop rhythm	Sepsis; *Staph. albus;* pneumonia

TABLE I—CONT'D

CASE NO. AND SEX	TYPE OF COARCTATION	PATENCY OF DUCTUS	DEGREE OF AORTIC CONSTRICTION	SIZE OF HEART	RIGHT VENTRICLE THICKNESS (CM.)	LEFT VENTRICLE THICKNESS (CM.)	ASSOCIATED CONGENITAL CARDIOVASCULAR ANOMALIES	MISCELLANEOUS X-RAY, EGG, ANGIOCARDIOGRAPHY, AND PLETHYSMOGRAPHY	DIAGRAM
8. M. H. female	Infantile	Closed	Severe stenosis; 0.5 cm. in diameter; aorta 1.5 cm. in diameter	Enlarged	0.75	1.5	Persistent left vena cava; hypoplasia of descending aorta	On fluoroscopy heart globular; enlarged to right and left X-ray: heart greatly enlarged to right and left; prominent hilar shadows	
9. M. B. female	Infantile	Wide; 1.0 cm. in diameter	Severe; abrupt narrowing	37.0 grams; 2 × normal; right ventricle greatly dilated	0.2	0.6	Patent foramen ovale; partial atelectasis of lungs	Fluoroscopy: heart enlarged to right and left; cardiac thrust; precordial bulging of chest X-ray: heart enlarged; bulge in region of pulmonary conus; aortic arch inconspicuous	
10. R. D. male	Infantile	Patent; 0.4 cm. in diameter	Severe constriction 0.5 cm. in circumference; aortic arch distal to left common carotid 1.2 cm. in circumference; aortic ring 2.0 cm. in circumference; sharp constriction	78 grams (normal = 20 grams)	0.9	0.7	Patent foramen ovale	Fluoroscopy: heart markedly enlarged to right and left ECG: right axis deviation; ST_1 depressed; ST_2 elevated; T_2 inverted; fluctuated for 4 weeks from severe failure to very mild	

TABLE I—CONT'D

CASE NO. AND SEX	AGE AT ONSET OF SYMPTOMS	AGE AT DEATH	CONDITION AT BIRTH	DIAGNOSIS MADE CLINICALLY?	BLOOD PRESSURE ARMS*	FEMORAL PULSATIONS	CLINICAL SIGNS OF HEART FAILURE					ASSOCIATED ILLNESSES
							RESPIRATORY DISTRESS	EDEMA	CYANOSIS	ENLARGED LIVER (NO. FINGERS BELOW COSTAL MARGIN)	MURMURS AND HEART SOUNDS GALLOP RHYTHM	
11. M.D.W. male	4 da. Birth weight 5 lb., 8 oz.	4 da.	Normal	No	Not determined	Not determinded	Severe	None noted	Slight cyanosis with gray mottling of skin; ashen-gray	2 fingers	None; heart sounds distant	Hemorrhagic disease of the newborn; hemorrhage in trachea, bronchi, and alveoli; sepsis(?)
12. D. E. P. male	10 da.	25 da.	Normal	Yes	130/88 R 130/88 L 158/105 L 170/100 R	Good: right leg 70/0; left leg 0/0	Severe; many moist râles in both lungs	Extending from hand to elbows and from feet to knees	Grayish cyanosis of lips and ears	2 fingers	No murmur; heart sounds muffled	Sepsis; acute atrophy of liver; glomerulo-nephrosis
13. J. R. F. male	3 da.	10 da.	Normal	Yes	130/150 systolic; no diastolic reading recorded	Good; not felt 12 hr. later; no B.P. obtained	Severe; râles in both lung fields	Skin edema, scrotal edema, and all extremities	Cyanotic mottling	3 fingers	None; heart sounds of good quality	Diarrhea; sepsis; rectal bleeding; aspiration of vomitus; bronchopneumonia; focal atelectasis; emphysema of all lobes of lungs

TABLE I—CONT'D

CASE NO. AND SEX	TYPE OF COARCTATION	PATENCY OF DUCTUS	DEGREE OF AORTIC CONSTRICTION	SIZE OF HEART	RIGHT VENTRICLE THICKNESS (CM.)	LEFT VENTRICLE THICKNESS (CM.)	ASSOCIATED CONGENITAL CARDIOVASCULAR ANOMALIES	MISCELLANEOUS X-RAY, ECG, ANGIOCARDIOGRAPHY, AND PLETHYSMOGRAPHY	DIAGRAM
11. M.D.W. male	Infantile	Wide; continuation of pulmonary artery	0.4 cm. in circumference; barely admits fine probe	Normal?	0.5	0.5	Interventricular septal defect; atelectasis of the lungs	Serosanguineous pleural effusion and peritoneal effusion	
12. D. E. P. male	Infantile	Wide; fusiform shape; 28 mm. in circumference; at widest point aortic orifice is 1.5 cm. in circumference	Moderately severe coarctation; 1.3 cm. in circumference; aortic ring is 2.2 cm. in circumference; aorta distal to ductus 2.3 cm.	50 grams (normal = 20 grams)	0.6	0.8	Patent foramen ovale, guarded type	ECG: marked right axis deviation; T_1 and T_2 inverted; T_3 upright; ST_3 depressed Fluoroscopy: heart greatly enlarged to right and left; thrombosis in superior mesenteric artery with foci of calcification and extending to include orifices of coeliac axis; right and left renal artery	
13. J. R. F. male	Infantile	Wide; 0.8 cm. in circumference	Severe; 0.3 cm. in circumference		0.6	0.5	Patent foramen ovale; bicuspid aortic valve	ECG: right axis deviation; QRS slurred Fluoroscopy: moderate enlargement to right and left (especially to the right)	

TABLE I—CONT'D

CASE NO. AND SEX	AGE AT ONSET OF SYMPTOMS	AGE AT DEATH	CONDITION AT BIRTH	DIAGNOSIS MADE CLINICALLY?	BLOOD PRESSURE ARMS*	FEMORAL PULSATIONS	CLINICAL SIGNS OF HEART FAILURE					ASSOCIATED ILLNESSES
							RESPIRATORY DISTRESS	EDEMA	CYANOSIS	ENLARGED LIVER (NO. FINGERS BELOW COSTAL MARGIN)	MURMURS AND HEART SOUNDS GALLOP RHYTHM	
14. K. S. F. female	Birth	7 da.	Cyanotic due to tongue swallowing	No	Not done	Good	None	None	Cyanosis due to obstruction of tongue; heart sounds of good quality	No	No	Hypognathus; swallows tongue; aspiration pneumonia; bronchopneumonia
15. W. K. S. female	Birth	44 da.	Cyanotic	No	105/? R	Good	Severe; fine crepitant râles over both lungs	Upper and lower extremities first, then generalized	Moderate to severe cyanosis turning to slatey gray	4 fingers	None at first; heart sounds of poor quality	Hepatitis; pyelonephritis; aspiration of vomitus; diaphragmatic hernia
16. L. H. S. male	Birth	10 da.	Difficulty breathing; cyanosis on crying	Yes	No B.P. obtainable on admission; B.P. 170/100 in right arm after clinical improvement	None; no B.P. obtained	Severe; improved with treatment; fine crepitant râles in both lungs	None	Mild cyanosis; legs same color as rest of body	3 fingers	Inconstant systolic precordial; gallop rhythm	Partial atelectasis in all lobes of lungs; food found in larynx
17. R. E. H. male	4 da.	35 da.	Normal	Yes	150/100 R 150/100 L	Palpable; no B.P. in legs could be ascertained	Severe; suppressed breath sounds over left lung field; gallop rhythm	Edema of face and generalized	Gray; cyanosis	4 fingers	Systolic murmur over precordium; not constant; heart sounds of fair quality	Diarrhea; pneumonia (?)

TABLE I—CONT'D

CASE NO. AND SEX	TYPE OF COARCTATION	PATENCY OF DUCTUS	DEGREE OF AORTIC CONSTRICTION	SIZE OF HEART	RIGHT VENTRICLE THICKNESS (CM.)	LEFT VENTRICLE THICKNESS (CM.)	ASSOCIATED CONGENITAL CARDIOVASCULAR ANOMALIES	MISCELLANEOUS X-RAY, ECG, ANGIOCARDIOGRAPHY, AND PLETHYSMOGRAPHY	DIAGRAM
14. K. S. F. female	Infantile	Wide; 0.8 cm. in circumference	Mild; 0.9 cm. in circumference; proximal aorta 1.8 cm. in circumference; descending aorta 1.5 cm. in circumference	Enlarged	0.6	0.6	Hypoplasia of the aorta; dilated right auricle; cleft soft palate; hypoplasia of mandible	Died of aspiration asphyxia; bronchopneumonia of all lobes of lung; focal atelectasis of lungs	
15. W. K. S. female	Infantile	Wide; 1.4 cm. in circumference; same as distal aorta	Severe; 0.2 cm. in circumference	50 grams	Right greater than left		Atresia of mitral valve; hypoplasia of left ventricle; interventricular septal defect; patent foramen ovale; bicuspid aortic valves	Fluoroscopy and x-ray showed a markedly enlarged heart ECG: marked right axis deviation; T_4 inverted	
16. L. H. S. male	Infantile	Slight; less than 0.1 cm. wide	Severe; 0.4 cm. in circumference; aortic orifice 1.7 cm.	70 grams	0.07	0.09	Large defect of foramen ovale; interventricular septal defect; hyperplasia of pulmonary artery	Fluoroscopy: heart enlarged to left (globular) X-ray: tremendous enlargement in all directions ECG: right axis deviation.	
17. R. E. H. male	Infantile	Wide; 1.0 cm. in circumference	Severe; 6 mm. in circumference; extends for 9 mm.; ascending aorta 1.6 cm. in circumference; descending aorta 1.6 cm. in circumference				Complete transposition of the great vessels; hypoplasia of right ventricle; interventricular septal defect; patent foramen ovale; aplasia of tricuspid valve	ECG: left axis deviation; QRS prolonged; marked left ventricular hypertrophy with myocardial damage Fluoroscopy: heart markedly enlarged to right and left Attempt at surgery: infant expired on opening thorax	

TABLE I—CONT'D

CASE NO. AND SEX	AGE AT ONSET OF SYMPTOMS	AGE AT DEATH	CONDITION AT BIRTH	DIAGNOSIS MADE CLINICALLY?	BLOOD PRESSURE ARMS*	FEMORAL PULSATIONS	CLINICAL SIGNS OF HEART FAILURE					ASSOCIATED ILLNESSES
							RESPIRATORY DISTRESS	EDEMA	CYANOSIS	ENLARGED LIVER (NO. FINGERS BELOW COSTAL MARGIN)	MURMURS AND HEART SOUNDS GALLOP RHYTHM	
18. H. D. W. male	10 da.	14 da.	Normal	Yes	100/80 R 100/80 L	Faint; B.P. not obtained	Severe; fine crepitant râles in right chest	None	None	3-4 fingers	Systolic; heart sounds poor quality; gallop rhythm	Atelectasis of lungs; death after angiogram
19. K. J. P. female	56 da.	67 da.	Normal	Yes	140/? R	Faint; B.P. not obtainable	Severe; fine râles over right chest	Edema of feet	Ashen-gray color	3 fingers	Systolic over precordium; loud	Diarrhea
20. A. J. B. female	Birth	6 da.	Cyanotic	No	Not done	Good; B.P. not done	Severe; fine râles over left posterior chest	Generalized	Cyanotic (blue)	2 fingers	None; heart sounds of good quality	Sepsis; atelectasis of left lung
21. J. A. B. male	Birth	22 da.	Cyanotic	No	100/? R	Good; B.P. left leg 90/?	Severe; crepitant râles over both lung fields	None	Peculiar gray color alternating with frank cyanosis	1-2 fingers	Systolic murmur over pulmonic area; not constant; heart sounds good quality	Diarrhea; focal atelectasis of lungs

*R = right arm; L = left arm.
†P.M.I. = point of maximal impulse.

TABLE I—CONT'D

CASE NO. AND SEX	TYPE OF COARCTATION	PATENCY OF DUCTUS	DEGREE OF AORTIC CONSTRICTION	SIZE OF HEART	RIGHT VENTRICLE THICKNESS (CM.)	LEFT VENTRICLE THICKNESS (CM.)	ASSOCIATED CONGENITAL CARDIOVASCULAR ANOMALIES	MISCELLANEOUS X-RAY, ECG, ANGIOCARDIOGRAPHY, AND PLETHYSMOGRAPHY	DIAGRAM
18. H. D. W. male	Infantile	Slight; barely admits probe	Severe; 0.3 cm. in diameter		0.7	0.5	Overriding aorta; patent foramen ovale; interventricular septal defect	X-ray: heart enlarged to right and left Angiogram, Plethysmograph studies: consistent with diagnosis of coarctation	
19. K. J. P. female	Infantile	Patent; no figures noted	Complete; diffuse	Enlarged markedly to left	1.0	0.8	Overriding aorta; absent right coronary artery; interventricular septal defect; bicuspid aortic valve; left subclavian artery given off by pulmonary artery; descending aorta is continuation of ductus arteriosus and pulmonary artery	X-ray ECG: right axis deviation Plethysmographic studies: consistent with diagnosis of coaretation	
20. A. J. B. female	Infantile	1.4 cm. in circumference	Mild; 0.5 in circumference; diffuse constriciton 1.1 cm. long; aortic valve 1.6 cm. in circumference	37 grams (normal = 18 grams)	0.2	0.3	Interventricular septal defect; patent foramen ovale; partial dextroposition of great vessels	Died 2 hr. after admission	
21. J. A. B. male	Infantile	Wide; 1.1 cm. in circumference; 0.8 cm. long	Mild coarctation; 0.9 cm. in circumference; diffuse; 1.3 cm. long; aortic ring 1.7 in circumference	28 grams (normal = 19 grams)	0.6	0.3	Large patent foramen ovale	Fluoroscopy: heart normal size ECG: right axis deviation; T_1 inverted	

Cyanosis.—Cyanosis was present in nineteen cases. In three instances (Cases 15, 20, and 21) it was present constantly since birth and was caused by other severe congenital anomalies. In another case episodes of cyanosis occurred soon after birth, due to hypoplasia of the mandible causing the tongue to fall back and block the air passages.

In fifteen cases a peculiar slaty gray or ashen-gray color was noted at some time during the period of observation of the infants. Cyanosis of the deep blue hue which was generalized and varied from moderately severe to severe was noted only in those infants who had associated major congenital abnormalities, e.g., dextroposition of the aorta.

None of the patients in this series showed any difference in intensity of cyanosis of the lower extremities as compared with that of the trunk and upper extremities. It has been pointed out[34] that in this condition where the ductus arteriosus is widely patent and opens into the aorta distal to the coaretation, cyanosis may be seen from the brim of the pelvis downward, including the lower extremities.

Enlargement of the Liver.—The liver was enlarged in twenty cases, extending from 2 to 8 cm. below the costal margin. Two infants who were not in congestive heart failure showed no hepatomegaly.

Edema.—In fourteen cases some form of edema was present. In five cases the edema was generalized. In seven cases there was a peculiar edema confined to the upper extremities from the elbows down and the lower extremities from the knee down. Facial edema was present in two infants.

Size of the Heart.—Cardiac enlargement was demonstrated clinically and roentgenologically in all but one case. Fluoroscopy usually revealed the heart to be tremendously enlarged to both right and left, often compressing the lungs in both bases.

Electrocardiographic Findings.—Electrocardiographs were obtained in thirteen patients. Right axis deviation was noted ten times and left axis deviation three times; myocardial damage was indicated in eight instances by notching and slurring of the QRS complex in two or more leads; low voltage of the QRS complex and T wave; inverted and diphasic T waves; notching, inversion, and peaking of the P waves.

Associated Illnesses.—No associated illnesses were present in four infants. The remaining eighteen were admitted to the hospital with severe cardiac failure plus definite evidence of an acute associated illness. Four infants had pneumonia; four had upper-respiratory infections; four had sepsis; four had diarrhea; two had an unexplained febrile illness; and two had hemorrhagic disease of the newborn infant. Although several of these had exhibited some cyanosis and/or grunting type of respiration since birth, the severe symptoms of frank cardiac failure did not become apparent until the complicating illness appeared. Evidently the associated illnesses played a definite role in precipitating cardiac failure.

CLINICAL DIAGNOSIS

The diagnosis was made clinically in fourteen of the twenty-two cases presented. We have been unable to find any prior report in the literature

of a clinical diagnosis of coaretation made in the newborn period corroborated by autopsy findings.

The criteria for diagnosis in the young infant are the same as for the older patient; namely, hypertension in the upper extremities and hypotension or unobtainable blood pressure in the lower extremities. The femoral pulse may or may not be present. Occasionally hypotension, unobtainable blood pressure, or absent femoral pulse in the lower extremities in the presence of a normal systolic pressure in the upper extremities may indicate the presence of coaretation of the aorta as in Cases 5 and 18.

Although hypertension is rare in the newborn infant and in early infancy, causes other than coaretation of the aorta must be ruled out. We consider a systolic pressure of 100 and diastolic of 70 as the upper limits of normal in the newborn period.

Hypertension during the first two or three days of life is most commonly due to pre-eclampsia or eclampsia in the mother. This hypertension subsides in a few days. Urinalysis reveals an increased number of red and white blood cells and a proteinuria. The blood pressure in the legs is higher than in the arms. These patients may, therefore, be easily differentiated from infants with coaretation of the aorta.

Acute glomerulonephritis with hypertension is occasionally seen in early infancy and is characterized by hypertension in the legs as well as in the arms, typical urinary findings of acute nephritis, and elevation of the blood nonprotein nitrogen. Head injuries with concussion and contusion of the brain or intracranial hemorrhage may cause hypertension in all four extremities. Chronic pyelonephritis, congenital polycystic kidneys, and other congenital anomalies of the kidneys are occasionally the cause of hypertension. In these cases the hypertension is usually not manifest until several months after birth and is present in all four extremities. Other manifestations of kidney disease or abnormality are present in the blood or urine.

As a working rule, the presence of hypertension in only the upper extremities of young infants in the absence of urinary or neurological findings is sufficient to establish a diagnosis of coaretation of the aorta. The diminution or absence of femoral pulse indicates the adult type or possibly the infantile type with a small or closed ductus. The presence of a good femoral pulse with hypertension in the upper extremities usually indicates the infantile type of coaretation.

PLETHYSMOGRAPHY AS AN AID IN DIAGNOSIS

This technique has been employed as an aid in the diagnosis of coaretation of the aorta in adults and children,[42, 43, 44] but has not been utilized in the study of infants. In this latter age group it may be of great value as it is easily carried out and is completely without harm to the patient.

The photoelectric plethysmograph as used here consisted of a 2.2 volt light source which was fitted in a small holder, so as to direct light through the part being studied to a photoelectric cell (Cetron 22-A.B.). The holders were applied to the central portion of the ears, hands, and feet. Density

changes were amplified and electrically transmitted to a Sanborn Cardiette galvanometer and then recorded on a kymographic camera. Pulse amplitude was used as a semiquantitative measurement of blood flow in the part. Measurements were made with the infant horizontal in a constant temperature room at 80° F.

In normal infants, as in adults, the pulse wave amplitude in the foot is the same or slightly less than in the hand, and in the ears it is greater than in either hand or foot. This is partially due to differences in thickness of the parts. Pulsation should be approximately equal in any of these parts compared to its opposite member. By measuring the time lag between hand and foot pulse, measured simultaneously and knowing the distance from hand to foot, estimation of pulse wave velocity can be made. In normal infants pulse wave velocity has been found to be 5 to 9 meters per second.[45]

Five infants with coarctation of the aorta were studied.* They ranged in age from 11 days to 8 months. The plethysmographic findings were similar to those reported in adults and children. Considerably less amplitude of the pulse wave contour was found in the feet than in the hands. The dicrotic notch was usually lost in the feet. Whereas the anacrotic limb is much steeper than the dicrotic in the normal pulse, in these patients both limbs tended to lose their steepness, and the anacrotic limb approached the dicrotic in degree of slope. By comparing the pulse in both hands and both ears, information was obtained as to whether or not the subclavian or carotid arteries were involved in the constriction.

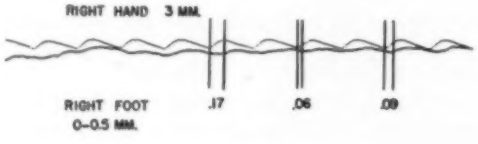

Fig. 2.—Microplethysmographic tracings in an infantile type of coarctation of the aorta.

The presence of a patent ductus arteriosus was indicated by an absent or small variable dicrotic notch, broadening of the wave apex, a tendency of the anacrotic and dicrotic limbs to be equal in slope.

A marked delay in pulse wave velocity was regularly found. In the five cases studied the velocity varied from 2.21 to 5.75 meters per second even in the face of hypertension.

Figure 2 is typical of the tracings obtained and shows considerable difference in amplitude between hand and foot pulses. The hand pulsation has a very rounded top and almost equal anacrotic and dicrotic limbs. The dicrotic notch is lost, indicating the presence of a patent ductus arteriosus.

*These studies were done by Dr. John A. Nuetzel, and Dr. Melvin Goldman of the Division of Hypertension of the Department of Medicine, Washington University School of Medicine.

ANGIOCARDIOGRAPHY

Visualization of the coarcted aorta in older children and adults is an established procedure. Its value lies in clearly demonstrating the site, severity, and extent of the narrowing. The retrograde arterial injection of radiopaque material has been found to give clearer visualization than the intravenous injection.[46] When deciding on the route of injection of the radiopaque material (70 per cent Diodrast) in these cases, the pathologic anatomy must be kept in mind.

In our series of patients sixteen of the twenty-one examined at autopsy had the infantile type of coarctation with the patent ductus emptying into the aorta beyond the site of coarctation. Therefore, if the intravenous route were used, a large portion of the Diodrast would pass directly from the pulmonary artery via the patent ductus into the descending aorta. The coarcted segment of aorta would be by-passed, and the small amount of Diodrast finally getting into the ascending aorta would not be in sufficient concentration to demonstrate the narrowing satisfactorily.

Very clear roentgenograms of the coarcted area may be obtained by the retrograde arterial injection technique (Fig. 3). The left brachial artery is usually the vessel of choice.

There are definite dangers in utilizing either method of visualization. The infant subjects are always either in, or closely bordering on, cardiac failure. Any sudden increase in intracardiac pressure may precipitate acute cardiac dilatation and death.

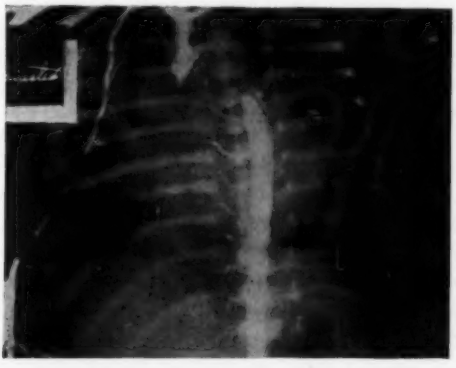

Fig. 3.—Retrograde visualization of the aorta in an infantile type of coarctation of the aorta.

It is our feeling that this method of diagnosis is not needed in this group of patients and should be avoided because of its potential danger.

CAUSE OF DEATH

In nineteen of the twenty-two cases, the direct or indirect cause of death was congestive heart failure. The picture of heart failure in these cases seems to fall in a definite pattern: namely, of severe cardiorespiratory distress with grunting rapid respirations; enlarged liver; peculiar ashen-gray color of

skin; edema; and tremendous enlargement of the heart to both the right and left.

In our experience one of the most common causes of cardiac failure in infants under 2 months of age has been coaretation of the aorta. Of the two deaths not directly due to cardiac failure, one infant died a few minutes after retrograde injection of 4 c.c. of 70 per cent Diodrast into the left brachial artery. The second infant died from prolapse of tongue with suffocation. In four infants the immediate cause of death was aspiration of vomitus with asphyxia. One infant died twenty minutes after the successful anastomosis of an arterial graft subsequent to excision of a diffusely coarcted aorta (Case 6). One infant died during an operation for correction of the coaretation.

PATHOLOGIC FEATURES

Type of Coarctation.—Post-mortem examination of twenty-one patients revealed fourteen with the infantile type, two with the adult type, and five with the combined adult and infantile type. It was impossible to differentiate the two groups by history, clinical course, or physical examination except for the presence of definite femoral pulsations. In each of the ten infants showing definite femoral pulsations, the infantile type of coaretation was present with a widely patent ductus arteriosus opening into the aorta distal to the constriction.

Degree of Constriction.—In eighteen infants the degree of coaretation was moderately severe to completely constricted. The moderately severe constriction is defined as one in which the cross-sectional area is at least 60 per cent narrower than the cross-sectional area of the aortic ring. By making a careful study of the degree of constriction and the blood pressure, we may conclude that in the absence of other severe cardiovascular anomalies the blood pressure is higher when the degree of constriction is greater (Table II). The highest blood pressure occurred in those infants where the aorta was completely constricted. This conclusion differs from the findings in the adult type of coaretation in patients 2 years old or older. Reifenstein and associates[22] report no significant differences in mean arterial pressures in relation to the various degrees of coaretation.

In the infantile type a sharp constriction was present in seven cases and diffuse type in seven. This finding is at variance with the oft quoted statement that the diffuse type of constriction is the usual finding in the infantile type coaretation.

Ductus Arteriosus.—The ductus arteriosus was patent in nineteen cases and completely closed in two cases. In the two instances where it was obliterated, one infant had an infantile coaretation and the other an adult type.

Cardiac Hypertrophy.—In every subject autopsied the heart was enlarged. The left ventricular wall was thicker than the right in nine infants, thinner than the right in eight cases, and the same thickness as the right ventricle in three cases. However, in all except three cases, the right auricle and ventricle were described as being more dilated than the left side of the heart,

In two of these exceptions where the left ventricle predominated, the infants were among the oldest patients in the series. In both cases the ductus arteriosus was obliterated. In the third instance there was a marked hypoplasia of the right ventricle.

Those patients with the greatest hypertrophy of the left ventricle showed roughly the following characteristics: (1) they were the longest surviving, (2) they had the narrowest diameter of the ductus, and (3) they had the highest blood pressures (Table II).

From these observations it is apparent that in young infants marked hypertrophy and dilation of both ventricles occur. Where the ductus arteriosus is widely patent, the greatest degree of right-sided dilation will occur. As the infant becomes older and the ductus arteriosus closes, the dilation and hypertrophy will become most marked in the left ventricle, and the blood pressure in the arms will also become higher.

Associated Congenital Cardiovascular Anomalies.—Associated minor congenital abnormalities (those compatible with adult life) were found in twelve of the twenty-one subjects autopsied. Associated major congenital anomalies were found in five patients. In four patients no other cardiovascular anomalies were found.

Among the minor cardiovascular anomalies found were patent foramen ovale in twelve cases, interventricular septal defect in nine cases, bicuspid aortic valve in six cases, mild hypoplasia of the aorta in two cases. Among the major congenital anomalies were overriding of the aorta in four cases, atresia of mitral valve with hypoplasia of left ventricle in one case, absent right coronary artery in one case, atresia of aortic arch in one case, hypoplasia of right ventricle with aplasia of tricuspid valve, one case.

The widely accepted idea that the infantile type of coarctation is usually associated with other grave congenital anomalies and is incompatible with life must be examined more closely. Abbott[16] in her series of eighty-two cases of the infantile type of coarctation reports an incidence of fifty cases or 60 per cent that were associated with other grave congenital anomalies. Grave anomalies included such conditions as septal defects. Others do not report as high an incidence. Blackford[2] in his series of thirty-eight cases of the infantile type reports an incidence of 10 or 25 per cent in which other grave anomalies existed. Benkwitz and Hunter,[23] in their review, report two cases of a total of twenty-six in which other grave anomalies existed. In our survey of twenty-one cases, 27 per cent of the patients had other grave cardiovascular anomalies.

DISCUSSION

Many infants under 2 months of age die with unrecognized coarctation of the aorta. In our experience during the past two years at the St. Louis Children's Hospital, coarctation of the aorta has been one of the most common causes of cardiac failure during the first two months of life. Most of the infants seemed normal at birth, but 78 per cent showed signs and symptoms of cardiac failure within fourteen days after birth. In 22 per cent cardiac de-

TABLE II. COMPARISON OF BLOOD PRESSURE WITH OUTSTANDING CLINICAL AND PATHOLOGIC FINDINGS

CASE NO.	B.P. UPPER EXTREM.*	CIRCUM. COARCTATION (MM.)	CIRCUM. DUCTUS (MM.)	FEMORAL PULSATIONS	TYPE AND CHARACTER OF COARCTATION	LIFE SPAN (DA.)	THICKNESS (MM.) OF L. VENTRICLE / THICKNESS (MM.) OF R. VENTRICLE	ASSOCIATED CONGENITAL ANOMALY. CAUSE OF DEATH
18 J. A. B.	100 / ?	9 Aortic ring 17	11	Good B.P. 90/?	Infantile Diffuse	22	3 / 6	Patent foramen ovale; aspiration pneumonia
15 H. W.	100 / 80	9	3	Faint	Infantile Diffuse	14	5 / 7	Dextroposition of aorta; interventricular septal defect; patent foramen ovale. Died after angiogram
13 W. K. S.	105 / ?	2	14	Good	Infantile Sharp	44	9 / 7	Atresia of mitral valve; hypoplasia of left ventricle; interventricular septal defect; patent foramen ovale
5 S. D. R.	110 / 85	11	6	Not felt	Adult and infantile Diffuse	52	8 / 12	Interventricular septal defect. Died of bronchopneumonia
12 D. E. P.	130 / 88 R 130 / 88 L	13 Ascending aorta 22	15	Good	Infantile Diffuse	25	8 / 6	Thrombosis of superior mesenteric artery including orifices of coeliac axis; both renal arteries; hepatic necrosis
7 B. S. W.	130 / 100 R 130 / 90 L	6 Diffuse ascending aorta 2 (circ.)	12	Definitely palpable	Adult and infantile Diffuse	28	5 / 6	Sepsis? Interventricular septal defect. Cardiac failure
8 M. H. B.	140 / 70	Abrupt narrowing	10	Good	Infantile Sharp	23		Patent foramen ovale; right ventricle hypertrophied; hemorrhagic disease of newborn. Diarrhea; bronchopneumonia

16 K. J. P.	140 ?	Atresia of arch	8	Faint	Infantile Diffuse	67	18 10	Dextroposition of aorta; aorta beyond left common carotid ended blindly; large patent ductus joined pulmonary artery to descending aorta from which the left subclavian artery arose; interventricular septal defect. Diarrhea and cardiac failure.
11 J. F.	130-150 ?	3	8	Good	Infantile Sharp	10	5 6	Patent foramen ovale; bicuspid aortic valve. Aspiration pneumonic, diarrhea, sepsis
3 S. R.	150/100 R 130/100 L	1.5	3	Faint	Adult and infantile Diffuse and sharp	42	9 7.5	Double coarctation; upper respiratory infection. Cardiac failure
17 R. E. H.	150/100 R 150/100 L	6 Ascending aorta 16	10	Definitely palpable	Infantile Diffuse	35		Hypoplasia of right ventricle and tricuspid valve; attempt at surgery. Infant expired on opening thorax
1 T. F. N.	160 88			Faint	Adult Diffuse	22	6 6	Bicuspid aortic valve; hemorrhagic disease of newborn. Cardiac failure
14 L. S.	170 100	4	3	Not felt	Infantile Sharp	40	10 9	Aspiration pneumonia; interventricular septal defect; marked patent foramen ovale
4 W. K.	160/90 R 190/90 L	Atresia	2.5	Faint	Adult and infantile Diffuse and sharp	30	8 7	Aspiration pneumonia; double coaretation; hypoplasia of common iliacs. Subarachnoid hemorrhage
6 M. H. M	180 130	Atresia	6	Faint	Adult Diffuse and sharp	35	6 5	Aortic arterial transplant performed. Infant died suddenly 20 minutes after operation

*R = right arm; L = left arm.

compensation occurred in the absence of any associated illness. Definite signs of decompensation were noted only after the onset of an associated illness (usually a bacterial infection) in 78 per cent of the cases. At the time of hospital admission every infant showed three or more of the following manifestations of cardiac failure: rapid, grunting respirations; marked cardiac enlargement; poor quality of heart sounds with a gallop rhythm; electrocardiographic evidence of myocardiac damage; hepatomegaly; cyanosis, and edema.

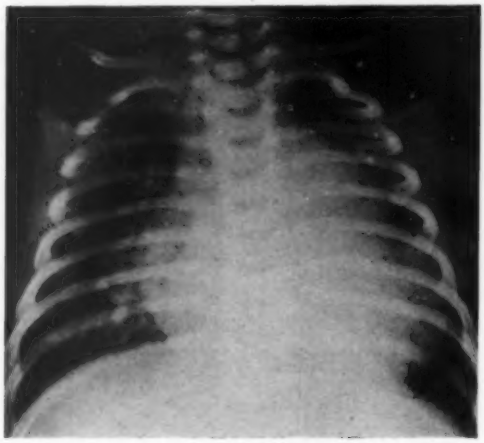

Fig. 4.—Posterior-anterior roentgenogram of the heart showing enlargement of the right auricle, right ventricle, engorgement of the pulmonary vessels, and prominence of the pulmonary conus.

In all of the patients examined, the forcefulness of the brachial artery pulsations was stronger than in the normal infant and more forceful than the femoral pulsations. Femoral pulsations were present in 45 per cent of the patients. This was readily explained by finding a widely patent ductus opening into the descending aorta. The presence of definitely palpable femoral pulsations indicates the presence of an infantile type of coaretation rather than an adult type in which the ductus arteriosus joins the aorta proximal to, or at the site of the coaretation.

In fourteen of the seventeen cases where blood pressure readings were recorded, hypertension was present in the upper extremities. In the three cases where the blood pressure was within normal limits, the absence of hypertension could be readily explained. In two infants, serious congenital defects were present. In the third, the constriction of the aorta was so mild that the cross-sectional area of the coaretation was more than 50 per cent of the cross-sectional area of the aortic ring.

From a clinical, pathologic, and therapeutic point of view our cases may be divided into these four groups:

Group I.—In this first group are the infantile and adult types of coarctation with a mild constriction of the aorta. The cross-sectional area of the coarctation is greater than 60 per cent of the cross-sectional area of the aortic ring. There is no elevation of blood pressure, and as a rule there are no signs or symptoms. This type is usually found accidentally at autopsy. Abbott,[6] in her 200 cases of adult type of coarctation, includes ten cases which belong in this category.

Animal experiments have been performed to show that mild constriction of a blood vessel does not affect the quantity of blood flow, therefore producing no hypertension proximal to the constriction. Gibbon, Hopkinson, and Churchill[36] in 1932 found that obstruction of the pulmonary artery up to 60 per cent of its cross-sectional area is without significant effect upon the arterial and venous pressures. A reduction in blood flow occurs when the occlusion is between 60 per cent and 85 per cent. The obstruction is fatal when 85 to 100 per cent of the pulmonary artery is occluded. Mann, Herrick, Essex, and Baldes,[36] in 1938, concluded that the carotid artery of a dog may be constricted a considerable extent before the blood flow is significantly reduced. The area of the lumen may be reduced 50 per cent without any change in blood flow. It can be reduced as much as 90 per cent before a 50 per cent reduction in blood flow occurs. Page[37] showed that from 65 to 80 per cent of the original cross-section of the aorta of dogs must be obliterated before a reduction in pressure occurs below the constriction.

Group II.—In this group are the infantile types of coarctation which have a moderately severe type of constriction in which sufficient reduction of blood flow occurs to cause hypertension. These babies at birth usually appear to be normal. Some arterial blood goes through the aortic constriction to the lower part of the body. Within a few days or weeks signs of cardiac failure usually appear. An intercurrent infection, diarrhea, malnutrition and/or other cardiovascular congenital abnormalities may hasten the onset of cardiac failure. The hypertension and consequent strain on the heart become more and more marked with increasing activity of the infant. They develop congestive heart failure and in spite of intensive treatment eventually die. They frequently linger on, going into and out of cardiac failure with no definite progress.

All of these cases in our series have been fatal. It is obvious that some infants with severe infantile coarctation do survive as this condition has been found in adults.[25, 26] These are the ones who have developed some collateral circulation in utero and especially during the early newborn period. They have not had complications precipitating periods of decompensation during early infancy. However, once cardiac failure sets in, the chances of recovery are extremely poor.

Group III.—In this group are cases of infantile coarctation where the aorta is severely constricted or entirely occluded. These infants are frequently born cyanotic and dyspneic or very soon develop these symptoms. Very little or no blood goes to the lower part of the body. The pulmonary artery is continuous with the descending aorta via the widely patent ductus arteriosus. They may survive for several days.

Group IV.—These infants have an adult type of coarctation with a severe or complete type of constriction. The great majority of these cases usually survive the newborn period. However, some infants may have a difficult time adjusting to the increased load on the heart due to hypertension and other associated conditions. The factors that precipitate cardiac failure in these infants are one or more of the following: the presence of acute infec-

tion, diarrhea or nutritional disturbance; poor establishment of collateral circulation in utero; and the presence of other congenital anomalies.

These babies are usually normal at birth and may develop cardiac failure within a week to several months. Once cardiac failure sets in, the prognosis is usually fatal. In adults with coarctation the development of cardiac failure is also of grave prognostic significance. Stewart and Bailey[38] and Stewart, Haskell, and Evans[39] have shown that enlargement of the heart and electrocardiographic changes of myocardial damage are of grave prognostic significance in coarctation.

TREATMENT

After studying the four groups, it is obvious that no therapy is indicated for patients in Group I. Patients in Group II are usually first seen in a critically ill condition with severe cardiac decompensation. Commonly there is an associated illness which has helped to precipitate the cardiac failure. The diagnosis can usually be made or suspected at once. Measures must immediately be taken to support the failing heart and to eliminate any associated illness. The same applies to patients in Group IV who develop cardiac failure.

Digitoxin, 0.1 mg. per each 3 kg. of body weight, is given as a digitalizing dose. This is preferably administered in divided doses over a twelve- to twenty-four-hour period but may be given within a three- to six-hour period if needed. After complete digitalization the patient is maintained on a daily dose of 10 per cent of the digitalizing dose. Oxygen therapy is of great importance and should be used early and intensively, even when the symptoms of cardiac decompensation are minimal. Peripheral and pulmonary edema are usually present, and to decrease the circulating blood volume, phlebotomy and mercurial diuretics are helpful. Actual venusection with bloodletting is a difficult procedure in infants. For that reason we prefer the bloodless type of phlebotomy where a blood pressure cuff is placed on each extremity, and three are inflated simultaneously to a pressure just above the diastolic level. In the legs the pressure usually has to be selected arbitrarily, approximately 50 to 60 mm. Hg. The cuffs are inflated in rotation, three at a time, and changed every fifteen minutes. Mercuhydrin is given intramuscularly in 0.25 c.c. amounts every twenty-four or forty-eight hours as long as needed. The use of intravenous fluids, blood, or plasma is very dangerous and has resulted in immediate fatalities due to further overloading of an already failing heart. The infants usually have great difficulty in taking feedings by mouth. For this reason, recently, regular bottle feedings have not been used during the period of cardiac failure. A No. 18 polyethylene tube is inserted through the nose, so that the end is at the cardia of the stomach. This may be left in place indefinitely without producing irritation. The formula is administered through the tube by gravity drip. The common complication of aspiration may be avoided by this method of feeding. A salt-free milk, Lonolac, is used as long as the edema and cardiac failure are present. When using mercurial diuretics and a salt-free milk, it is essential to watch the serum carbon diox-

ide and chlorides carefully. Under these circumstances they are occasionally seen to drop to dangerously low levels which, if uncorrected, may lead to death.

The associated illness is usually a bacterial infection. If possible, the exact bacterial etiology should be determined. This is almost never possible without a period of twenty-four to forty-eight hours for growth of cultures. Consequently, they should be covered as completely as possible with penicillin, streptomycin, and probably Chloromycetin or aureomycin until an exact bacteriologic diagnosis has been established. The sulfonamides should be used with extreme caution during the early period because of lack of knowledge of the individual child's renal function.

With this therapy a few of our patients showed a period of temporary improvement for a few days to a few weeks. However, once cardiac failure developed, they all eventually succumbed.

The application of surgery to this problem is the only method by which a cure of the coarctation may be achieved. Heretofore, this has been reserved for patients in childhood or adult life. Unfortunately, many patients never live to this age, so that we are forced to consider measures applicable to this early age group.

Three surgical techniques are used for coarctation of the aorta at present. Blalock and Park[40] devised the by-pass operation in which the left subclavian artery was severed as high in the neck as possible and the distal end anastomosed to the aorta below the point of coarctation. This is not a feasible procedure in small infants because of the very small size of the subclavian artery; the subclavian artery is frequently involved in the coarctation, and the coarcted segment is frequently too long to be bridged in this manner. The second technique is the operation devised separately by Gross[18] and Craaford[17] in which the coarcted segment is resected and the two ends of the aorta brought together in an end-to-end anastomosis. This procedure is ideal in the adult type of coarctation, but as most infants who develop cardiac failure have the infantile type, the length of the coarcted segment precludes bringing the two ends together in a primary anastomosis. The third type of operation devised by Gross[21] consists in resecting the coarctation and bridging the gap with an arterial graft obtained from another patient. This has been done successfully in several older patients, and this is the procedure which seems to hold most promise of success in infants. To achieve a successful operation, there must be sufficient collateral circulation to carry a minimally adequate supply of blood to the lower part of the body during the few minutes while the aorta is completely occluded. In one of our cases (M. H. M.), this operation was done by Dr. Thomas H. Burford. The coarcted segment of aorta was removed, and an arterial graft sutured in its place. The aorta was completely occluded for fifteen minutes during which time the heart continued to beat strongly and rhythmically. The clamps were removed, and blood coursed through the anastomosis with no leakage. He did well for fifteen or twenty minutes longer, and just as the skin incision was being closed, his heart suddenly stopped. At post-mortem examination the anastomosis was intact. It is felt that the cause of death was ventricular fibrillation.

In view of the extremely grave prognosis in these infants once cardiac enlargement and decompensation have occurred, they should be treated vigorously by medical measures. As soon as their condition has improved maximally, so that the heart is compensating, and they may be considered operable, we feel that this type of operation should be carried out. Unless the infant dies within the first few days after medical treatment has been instituted, two to three weeks are usually necessary before he is ready for any type of surgical procedure.

If routine blood pressure studies were made, and femoral artery pulsation determined on all newborn infants, many with asymptomatic coaretation of the aorta, occurring mainly in Group IV, would be discovered. These infants have adequately developed collateral circulation and have hypertension in the upper extremities but show no evidence of cardiac enlargement or decompensation. There would be no need for therapy other than careful observation and prevention of infections, unless progressive cardiac enlargement should be noted. The prophylactic use of oral penicillin may be of value and is worth while during the first six to twelve months of life.

SUMMARY

1. A review of the literature on coaretation of the aorta in children has been presented.

2. Twenty-two cases of coaretation of the aorta in infancy have been reviewed. Twenty-one of them were autopsied and are presented in Table I.

3. Fourteen of the twenty-two cases of coaretation were diagnosed correctly prior to autopsy.

4. Hypertension in the upper extremities was present at birth or very soon thereafter in fourteen of seventeen cases in which blood pressure readings were determined. Hypotension or absent blood pressure in legs was noted in every case.

5. Definitely palpable femoral pulses were noted in the infantile type of coaretation associated with a large patent ductus.

6. One of the most common causes of cardiac failure in infants under 2 months of age is coaretation of the aorta. Cardiac failure occurred in all of our cases.

7. Cardiac failure in these infants presents a characteristic clinical picture.

8. Once cardiac failure occurred, the prognosis was fatal in all cases.

9. The medical management of cardiac failure is discussed in detail.

10. Early surgical repair of coaretation in these infants is discussed and advised under certain conditions.

11. The presence of other severe congenital abnormalities of the heart and great blood vessels was noted in 27 per cent of the cases.

12. Routine blood pressure examination and palpation for femoral pulses is advised as part of the examination of every newborn and young infant.

The early diagnosis of coarctation of the aorta before the onset of cardiac failure may be lifesaving. Prevention of infection in these infants may help avert cardiac failure.

REFERENCES

1. Nelson, Waldo E., ed.: Textbook of Pediatrics (Mitchell-Nelson), ed. 4, Philadelphia, 1946, W. B. Saunders, p. 825.
2. Blackford, L. M.: Arch. Int. Med. **41**: 702, 1928.
3. Evans, William: Quart. J. Med. **2**: 1, 1933.
4. Abbott, M. E.: Atlas of Congenital Heart Disease, New York, 1936, American Heart Association.
5. Perlman, L.: Am. Heart J. **28**: 24, 1944.
6. Abbott, M. E.: Am. Heart J. **3**: 381, 1928.
7. King, J. T.: Arch. Int. Med. **38**: 69, 1926.
8. Lewis, Thomas: Heart **16**: 205, 1931.
9. Paris, M.: J. de chir. de Desault **3**: 107, 1791.
10. Eisenberg, G.: J. PEDIAT. **13**: 303, 1938.
11. Blumenthal, S., and Davis, D. B.: Am. J. Dis. Child. **62**: 1224, 1942.
12. Wilson, T. E.: Med. J. Australia **1**: 589, 1940.
13. Rhodes, P. H., and Durbin, E.: Am. J. Dis. Child. **64**: 1073, 1942.
14. Schwartz, S., and Greene, D.: Am. Heart J. **23**: 99, 1942.
15. Gross, R. E.: J. A. M. A. **139**: 285, 1949.
16. Abbott, M. E.: Modern Medicine, in Osler and McCrae: Monograph on Congenital Heart in Modern Medicine, vol. 4, ed. 3, Philadelphia, 1927, Lea & Febiger.
17. Craaford, C., and Nylin, G.: J. Thorac. Surg. **14**: 347, 1945.
18. Gross, R. E., and Hufnagel, C. A.: New England J. Med. **233**: 287, 1945.
19. Potts, W. J., Smith, S., and Gibson, S.: J. A. M. A. **32**: 627, 1946.
20. Clagett, O. T.: Proc. Staff Meet., Mayo Clin. **22**: 131, 1947.
21. Gross, R. E., Hurwitt, E. S., Bill, A. H., and Pierce, E. C.: New England J. Med. **239**: 578, 1948.
22. Reifenstein, G. H., Levine, S. A., and Gross, R. E.: Am. Heart J. **33**: 146, 1947.
23. Benkwitz, K. B., and Hunter, W. C.: Am. J. Path. **13**: 289, 1937.
24. Sala, A. M., and Nachamie, I.: Arch. Int. Med. **43**: 420, 1929.
25. Johnson, J., and Kirby, C. K.: Ann. Surg. **127**: 1105, 1947.
26. Adams, H. D., Rutledge, D. I., and Souders, C. R.: J. A. M. A. **139**: 6, 1949.
27. Ulrich, Henry L.: Am. Heart J. **75**: 641, 1931-32.
28. Bonnett, L. M.: Rev. de méd., **23**: 108, 1903.
29. Hisbut, P. A.: Arch. Path. **35**: 717, 1943.
30. Ingham, D. W.: New York State J. Med. **39**: 1865, 1939.
31. Ballantyne, E. N.: Am. J. Dis. Child. **50**: 642, 1935.
32. King, J. T.: Ann. Int. Med. **10**: 1802, 1937.
33. Smith, C. A.: The Physiology of the Newborn Infant, Springfield, Ill., 1946, Charles C Thomas, Publisher, p. 95.
34. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund, p. 491.
35. Gibbon, J. H., Jr., Hopkinson, M., and Churchill, E. D.: J. Clin. Investigation **11**: 543, 1932.
36. Mann, F. C., Herrick, J. F., Essex, H. E., and Baldes, E. J.: Surgery **4**: 249, 1938.
37. Page, I. H.: Am. Heart J. **19**: 218, 1940.
38. Stewart, M. J., and Bailey, R. L.: J. Clin. Investigation **20**: 9, 1941.
39. Stewart, H. J., Haskell, H. S., and Evans, W. F.: Am. Heart J. **28**: 217, 1944.
40. Blalock, A., and Park, E. A.: Ann. Surg. **119**: 445, 1944.
41. Bing, R. J., Handelsman, J. C., Campbell, T. A., Griswold, H. E., and Blalock, A.: Tr. Am. S. A. **66**: 484, 1948.
42. Megibou, R. S., and Feitelberg, S.: Am. J. Med. **4**: 798, 1948.
43. Goldman, M. L., and Schroeder, H. A.: Am. J. Med. (in press).
44. Hartmann, A. F. (Chief of Staff): Conference at St. Louis Children's Hospital, J. PEDIAT. **32**: 26, 1948.
45. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, ed. 3, Baltimore, 1943, William Wood & Company, pp. 252-257.
46. Carson, M. J., and Burford, T. H.: J. PEDIAT. **33**: 675, 1948.

PROTHROMBIN IN THE NEWBORN INFANT

V. Further Observations on the Nature of Prothrombin in the Newborn Infant: Comparative Effect of Storage on Prothrombin of the Newborn Infant and Normal Adult

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WITH the discovery of vitamin K and its relationship to prothrombin, increased interest has centered about the mechanism of clotting. Vitamin K is necessary for the formation of prothrombin. The latter is produced through the intermediary action of the liver and is necessary for the formation of a clot. Vitamin K is fat-soluble and is found in many foods, particularly the green, leafy vegetables. It is also produced in the gastrointestinal tract as a result of bacterial metabolism. Vitamin K has been isolated and found to contain a quinoid structure. A number of synthetic water-soluble naphthoquinone compounds having antihemorrhagic vitamin K activity are now available for oral or parenteral administration. A hypoprothrombinemia may be produced as a result of failure of absorption of vitamin K through the gastrointestinal tract or as a result of liver damage.

The simple classical theory that two steps are involved in clot formation, namely,

(1) prothrombin + calcium + thromboplastin → thrombin
(2) thrombin + fibrinogen → fibrin (clot)

is undergoing re-evaluation.

Recently, Quick[1-3] suggested that prothrombin is not a single substance but is composed of three factors. One factor he has named the "labile factor," which deteriorates on storage. The remaining two, prothrombin component A and prothrombin component B, are diminished by Dicumarol and are absorbed by agents such as aluminum hydroxide and tricalcium phosphate. The decrease in prothrombin activity of stored plasma is attributed to the decrease in the labile factor of prothrombin. He has demonstrated that the addition of plasma, which had been treated with aluminum hydroxide, will restore prothrombin activity to stored plasma.

This view has been questioned by other investigators. Seegers, Loomis, and Vandenbelt[4] claim to have isolated prothrombin as a single pure substance which is stable.[4, 5] The apparent decrease in prothrombin activity of stored plasma is attributed by Loomis and Seegers[6] to the effects of storage on plasma fibrinogen activity.

The presence of an additional factor in the clotting process was described by Ware and Guest,[7] and Seegers.[8] This factor, designated Ac-globulin (Accelerator-globulin), is present in plasma. It is stable and accelerates the formation of a clot. The liberation of thromboplastin from platelets and tissue juices

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initiates the clotting process. Some of the newly formed thrombin activates plasma Ac-globulin to serum Ac-globulin which in turn accelerates the formation of further thrombin.

Recently, a serum factor labelled SPCA (serum prothrombin conversion accelerator) which accelerates the conversion of prothrombin to thrombin by thromboplastin and calcium has been described by Alexander, De Vries, and Goldstein.[9]

In addition, a Factor V, necessary for the conversion of prothrombin to thrombin in the presence of thromboplastin and calcium, has been described by Owren[10] as being present in plasma.

The evidence available at the present time is inadequate for any conclusions regarding the identity of these accelerator factors.

Quick[11] has very recently postulated the existence in plasma of a precursor of thromboplastin, namely, thromboplastinogen. This thromboplastinogen is converted to the active form thromboplastin by an enzyme, thromboplastinogenase, derived from platelets. In hemophilia, the congenital deficiency or complete absence of thromboplastinogen results in insufficient thrombin formation because of incomplete conversion of prothrombin to thrombin.

In addition to accelerating factors, inhibiting factors, such as heparin, antithromboplastin, and antithrombin, are known to be present in blood.

To this complex picture is added the further complication that, in contrast to normal adults in whom a hypoprothrombinemia is an extreme rarity, infants demonstrate a decrease in prothrombin concentration fairly consistently in the neonatal period. The cause of this hypoprothrombinemia is not known, although numerous theories have been advanced. A possibility exists that this apparent hypoprothrombinemia may represent a qualitative or physiologic difference of prothrombin in newborn infants from that of adults. Previous studies by Kove and Siegel[12] have suggested the qualitative and physiologic identity of prothrombin in adults and newborn infants because of the similarity of reaction of their plasma prothrombin to serial dilution, in the clotting process. It was demonstrated that the graphs of the prothrombin clotting times of serial dilutions of plasma of normal adults and newborn infants followed similar hyperbolic curves. Furthermore, this similarity of reaction existed regardless of the presence or absence of a hypoprothrombinemia in the infants, and irrespective of the natural origin of prothrombin in the infants or its production by vitamin K therapy.

Of considerable practical value, because of the importance of transfusions as a therapeutic measure, is information concerning the effect of storage upon the prothrombin content of blood. It is known that the prothrombin activity of blood or plasma diminishes on storage. However, the manner and rate with which this depression progresses has aroused some controversy.

A rapid increase in prothrombin clotting time (decrease in prothrombin concentration) of stored bank blood was noted by Rhoads and Panzer[13] using the one-stage method of Quick. On the other hand, Lord and Pastore,[14] using the two-stage method of Warner, Brinkhaus, and Smith,[15] found only a slow de-

crease in prothrombin concentration to 60 per cent after three weeks in bank blood stored at 2-4° C. Ziegler and associates,[16] using the latter two-stage method, found a slow decrease in prothrombin concentration of bank blood to 40 per cent after 36 days' storage. Quick[1] has described a prompt and marked depletion of the labile factor of prothrombin on storage. Fahey, Ware, and Seegers[17] maintain that stored prothrombin remains constant for at least three weeks; however, a factor designated by them Ac-globulin (Accelerator-globulin) diminishes on storage to 55 per cent after two weeks and to 30 per cent after three weeks. If a loss of prothrombin activity occurs in plasma prothrombin, it would appear of considerable importance to know how rapidly and in what manner this decrease progresses.

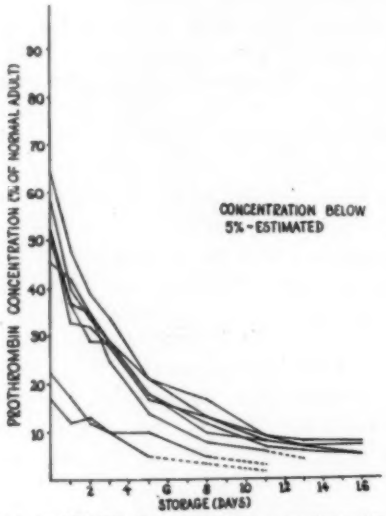

Fig. 1.—Effect of storage at 10°-20° C. upon plasma prothrombin concentration of the eight normal newborn infants in Group I.

The purpose of the present investigation was twofold. First, the comparative effect of storage at low temperature upon plasma prothrombin activity of newborn infants and normal adults was studied. This was done in an attempt to add further information to the problem of whether or not the prothrombin in the newborn infant is qualitatively and physiologically similar to that in the adult. Second, the effect of storage upon prothrombin activity of plasma was observed, so as to enable more effective use of blood or plasma as a source of prothrombin in transfusions.

To obtain this information, fresh plasma specimens from a group of normal adults and newborn infants were stored at low temperature and prothrombin determinations were performed on each specimen at varying intervals thereafter. It was also felt desirable to know whether the administration of vitamin K altered the effect of storage on the prothrombin activity of the plasma. There-

fore, prothrombin determinations were done similarly on a second group of stored plasma specimens of newborn infants who had received vitamin K at birth, and normal adults. The effects of storage upon the plasma prothrombin of the two groups of infants and adults were evaluated from graphs drawn to demonstrate the progressive decrease in prothrombin concentration.

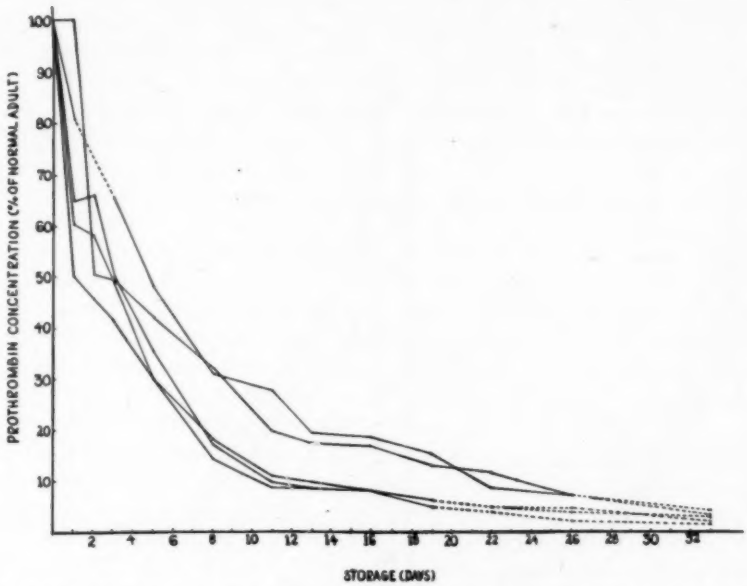

Fig. 2.—Effect of storage at 10°-20° C. upon plasma prothrombin concentration of the five normal adults in Group I.

METHOD OF STUDY

Prothrombin determinations were made on blood drawn from a group of eight newborn infants, less than 48 hours of age, who had not previously received vitamin K and whose mothers had not received vitamin K before delivery. At the same time, prothrombin determinations were made on blood drawn simultaneously from five normal adults. The plasma specimens of this group of eight newborn infants and the five normal adults, designated as Group I, were then stored together at a temperature range from 10° to 20° C. Determinations of prothrombin were made (on these plasmas) at varying intervals over a period of 16 days for the newborns and 33 days for the adults. The more extended period of determinations on the adult plasmas was employed in order to reach the same comparatively low prothrombin concentrations attained by newborn infants in a shorter period of time. It also permitted an observation of the effect of prolonged storage upon the prothrombin of adult plasma.

To determine whether vitamin K altered the effect of storage on prothrombin, plasma specimens were obtained from a second group of ten newborn infants

and four normal adults, designated as Group II, and prothrombin determinations were made. These infants varied in age from 1 to 6 days, and each had received intramuscularly, within one hour of birth, 5 mg. of a synthetic water-soluble vitamin K compound (2-methyl-1, 4-naphthohydroquinone diphosphoric ester tetrasodium salt). The plasma specimens were then stored under the same conditions as described for Group I, and repeated determinations were made over a period of 11 days.

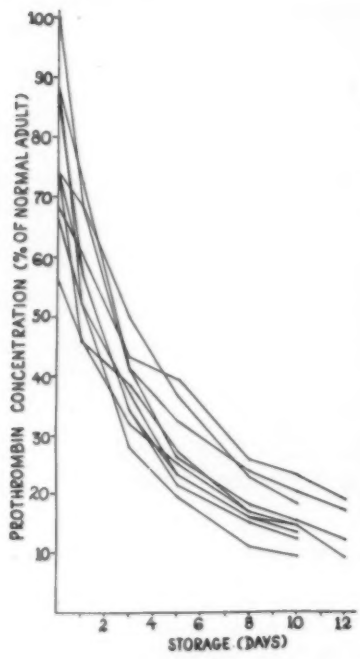

Fig. 3.

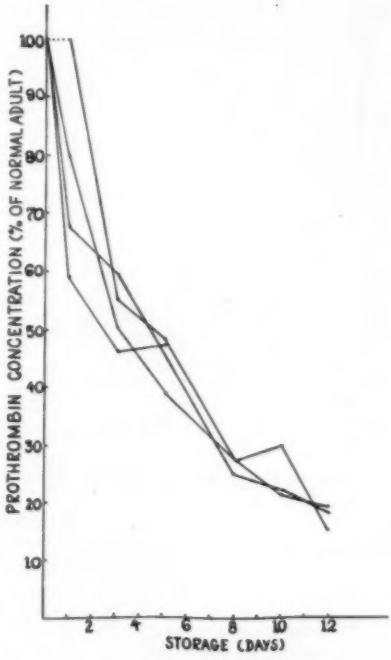

Fig. 4.

Fig. 3.—Effect of storage at 10°-20° C. upon plasma prothrombin concentration of the ten normal newborn infants in Group II who had received vitamin K intramuscularly at birth. [Vitamin K, 5 mg. of a synthetic water soluble compound (2-methyl-l, 4-naphthohydroquinone diphosphoric ester tetrasodium salt).]

Fig. 4.—Effect of storage at 10°-20° C. upon plasma prothrombin concentration of the four normal adults in Group II.

The method of Quick[18] was used in determining the prothrombin clotting time. Blood samples were drawn, 2.25 c.c. from infants using the internal or external jugular vein and 4.5 c.c. from adults. These were added to 0.25 c.c. and 0.5 c.c. of 0.1 molar sodium oxalate, respectively. Plasma for prothrombin determination and storage was obtained by centrifugation. To 0.1 c.c. of plasma was added 0.1 c.c. of thromboplastin in a small test tube, 7.5 cm. long and with an internal diameter of 0.85 cm. The tube was immersed in a water bath maintained at 35°-40° C. By blow pipette 0.1 c.c. of 0.025 molar calcium chloride was then added. The time required for the formation of a clot was determined

by stop watch and was recorded as prothrombin clotting time. The end point for the formation of a clot was established by the use of a glass rod curved to a hook at one end, because this method was found to yield a sharper end point for clot formation than the tilt tube method. (All determinations were performed by the authors.)

The prothrombin concentration was determined from a curve of serial dilutions of normal adult plasma for each thromboplastin preparation employed, as recommended by Quick.[18] It should be emphasized at this point that prothrombin concentration is not a quantitative measure of actual concentration, but rather a summation of the factors of concentration and its convertibility to thrombin in the clotting mechanism. It is expressed as percentage concentration of the normal adult plasma.

Prothrombin-free plasma was used as diluent in preparing the dilutions of adult plasma to 80, 60, 40, 20, 10, and 5 per cent. The dilution curve of normal adult plasma was constructed from the prothrombin clotting times obtained for each dilution. The prothrombin-free plasma was obtained from pooled plasma of three adults by the barium sulfate precipitation method.[19] The prothrombin-free plasma as a diluent was found to yield sharper and firmer clots than saline, particularly in the higher dilutions. This was to be expected, since dilution with prothrombin-free plasma will not result in dilution of other factors, such as fibrinogen, which are important in clot formation.

The value of reporting results as percentage concentration of normal adult plasma, in addition to prothrombin clotting time, cannot be over-emphasized, for this is the only way in which results can be evaluated and compared. The prothrombin clotting time of any plasma will vary with the potency of the thromboplastin preparation employed, being shorter for more potent thromboplastin preparations. The thromboplastin preparations in common use yield prothrombin clotting times of 12 to 25 seconds for normal adult plasma.

The dilution curve of the normal adult plasma permits one readily to convert a result in terms of prothrombin clotting time to prothrombin concentration (percentage of the normal adult). Results expressed in terms of prothrombin clotting time alone may convey a false picture of the concentration to all but those thoroughly familiar with the subject, because of the hyperbolic shape of the dilution curve (Figs. 5 and 6).

The thromboplastin preparation used was a stable rabbit brain suspension.* Repeated determinations on plasma freshly drawn from the same subject demonstrated that the thromboplastin, stored at temperatures ranging from 10° to 20° C., maintained its potency unchanged for at least one month. The stability of this thromboplastin obviated the necessity of making a new serial dilution curve of the normal adult plasma for each day of prothrombin studies, as is required for other thromboplastin preparations. As a result, it was only necessary to check the potency of the thromboplastin prior to any series of determinations. Repeated and thorough trial studies revealed this preparation to be reliable, and yielded consistent results which could be reduplicated. Two separate batches of this thromboplastin were used, one for each of the two groups

*Kindly furnished by Schieffelin & Company.

TABLE I. EFFECT OF PLASMA STORAGE AT 10° TO 20° C. UPON PROTHROMBIN CLOTTING TIME AND PRO (THROMBOPLASTIN No. 1 WAS USED

DURATION OF PLASMA STORAGE (DAYS)	INFANTS* CASE 2 (AGE 16 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 3 (AGE 16 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 4 (AGE 16 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 5 (AGE 17 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 6 (AGE 24 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 7 (AGE 29 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)
Fresh plasma	17.4	50	16.6	58	15.6	64	17	52	31	22	37	17
1	21	37	20	40	18	48	21	37	36	17	50	12
2	24.8	29	22.6	34	20.4	39	22	35	51	12	45	13
3	25.2	29	25	29	22.6	34	25.2	29	57	10	55	10
5	32.8	18	35	18	30.6	21	30.8	21	89	5	54.8	10
8	57	10	51	12	45.2	13	35.2	17	165	<5	98.6	5
11	72	8	82.2	7	68.4	8	61.2	9	360+	<5	140	5
13	85	7	88	6	85	7	80	7				
16			92	5	86	7	92	5				
19												
22												
26												
33												

P.C.T. = Prothrombin clotting time.
P.Conc. = Prothrombin concentration,
% N.A. = Percentage of normal adult concentration,
Sec. = Seconds.
†Prothrombin determinations on fresh plasma only.

TABLE II. EFFECT OF PLASMA STORAGE AT 10° TO 20° C. UPON PROTHROMBIN CLOTTING TIME AND PRO AND THE 4 NORMAL ADULTS IN GROUP II. (THROMBOPLASTIN

DURATION OF PLASMA STORAGE (DAYS)	INFANTS* CASE 1 (AGE 27 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 2 (AGE 38 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 3 (AGE 55 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 4 (AGE 67 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 5 (AGE 74 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 6 (AGE 88 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)	CASE 7 (AGE 95 HR.) P.C.T. (SEC.)	P. CONC. (% N.A.)
Fresh plasma	17.6	68	17.8	66	16.2	86	19.6	56	17	74	17	74	17	74
1	18.4	60	21	52	19.4	57	23	46	19.4	57	23.2	46	17.6	68
3	24.2	43	27.2	37	28.8	34	30	32	28.8	34	26.8	38	21.4	50
5	26	39	39	23	39	23	35.8	25	42.4	21	34.8	27	28	36
8	35.4	26	66	16	64.6	16	57	17	70	15	60	17	39	23
10	39	23	81	13	79	14	77.2	14	93.2	12	79.6	14	51	18
12	47.6	19			113	9								

P.C.T. = Prothrombin clotting time.
P.Conc. = Prothrombin concentration,
% N.A. = Percentage of normal adult concentration,
Sec. = Seconds.
*Each infant had received, intramuscularly, a synthetic water-soluble vitamin K compound (5 mg.
†Prothrombin determinations on fresh plasma only.

studied. The thromboplastin (No. 1) used for Group I yielded a value of 13 seconds for normal adult undiluted plasma. The value for normal adult plasma obtained with the thromboplastin (No. 2) employed for Group II was 15.8 seconds. The prothrombin clotting times of serial dilutions of each of the two thromboplastin preparations are shown in Table III and Table IV. The curves of serial dilution of normal adult plasma for each of the two thromboplastin batches (No. 1 and No. 2) used, and from which percentage prothrombin con-

THROMBIN CONCENTRATION OF THE 8 NORMAL NEWBORN INFANTS AND 5 NORMAL ADULTS IN GROUP I. IN PROTHROMBIN DETERMINATIONS.)

CASE 8 (AGE 36 HR.)		CASE 10 (AGE 46 HR.)		ADULTS										ADULT CONTROL†	
				CASE 11		CASE 12		CASE 13		CASE 14		CASE 15		CASE 16	
P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)
18.2	45	17	52	12.8	100+	12.4	100+	13.3	99	12	100+	12.4	100+	13	100
19	42	23	33	17.4	50	16	60	14	80	15.6	64	12.6	100	12.6	100+
22	35	23.4	32	18.2	45	16.2	57	13.2	100	15.2	65	17.4	50	13.4	99
27.4	25	26	28	19.6	41	18	48	15.6	64	17.6	50	17.8	49	13	100
42.6	14	36.2	17	25	29	25	29	18.4	48	22.2	35	19.4	41	12.6	100+
65	8	45.4	13	43.8	13	36.8	17	24.6	30	38	16	23.8	31	13.2	99
90	6	59.8	9	70	8	57.2	10	27	26	61	9	32.4	18	12.6	100+
107	<5	65	8	74	7	67	8	34.2	18	74	7	37.8	16		
		70	8	77	7	74	7	36.4	17	77	7	41	15	12.8	100+
				90	6	88	6	40.8	15	100	5	44	13		
				105	<5	105	<5	58.2	9	133	<5	51.8	12	13.2	100
				125	<5	110	<5	80	7	285	<5	75	7		
				215	<5	295	<5	120	<5	450	<5	135	<5	13	100

THROMBIN CONCENTRATION OF THE 10 NEWBORN INFANTS WHO HAD RECEIVED VITAMIN K AT BIRTH, No. 2 WAS USED IN PROTHROMBIN DETERMINATIONS.)

CASE 8 (AGE 111 HR.)		CASE 9 (AGE 123 HR.)		CASE 10 (AGE 133 HR.)		ADULTS								ADULT CONTROL†	
						CASE 11		CASE 12		CASE 13		CASE 14		CASE 15	
P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)
15.4	100+	16	88	16	88	15.8	100	15	100+	15.8	100	15.4	100+	15.8	100
17.6	68	17.2	72	20.8	52	17.4	68	15.6	100+	18.8	59	16.4	80	15.2	100+
25	41	25	41	33.8	28	18.6	59	20	55	23.2	46	21.4	50	15.8	100
36	26	30.4	32	49.6	19	23.4	45	22	48	22.8	47	26.2	39	15.8	100
52	18	38.6	24	96.8	11	37.2	25	34.4	27			34	27	15.6	100+
71	15	44.4	20	112	9	42	22	32	30			42.6	21	15.4	100+
95	12	59	17			51	18	67	15			47.2	19	15.4	100+

of 2-methyl-1, 4-naphthohydroquinone diphosphoric ester tetrasodium salt).

centration (of the normal adult) was computed for all prothrombin clotting time determinations, are shown in Figs. 5 and 6.

RESULTS

The results of prothrombin determinations on the stored plasma specimens of the newborn infants and adults in Group I are recorded in Table I, and Figs. 1 and 2. The results for Group II are recorded in Table II, and Figs. 3 and 4.

On storage, a loss occurs in plasma prothrombin concentration, which follows a hyperbolic curve. This was true for the plasma of normal adults, newborn infants who had received vitamin K, and newborn infants who had not received vitamin K, as shown in Figs. 1, 2, 3, and 4. It is to be noted that, if a point on any one curve is superimposed upon the same percentage concentration on any other curve, the remainder of the curves approximately coincide. Curves which started at a low concentration, such as those for some of the untreated newborn infants in Group I (Fig. 1), could be superimposed for similar values on curves of the adults which started at 100 per cent concentration (Figs. 2 and 4).

Regardless of the source of the plasma specimens, those with a high initial prothrombin concentration demonstrated a somewhat rapid decrease during the first few days. Thereafter, the diminution proceeded more slowly. In the in-

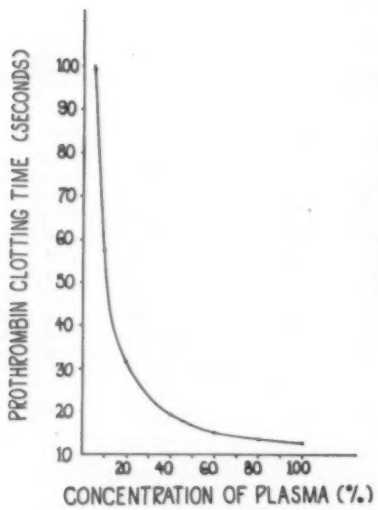

Fig. 5.

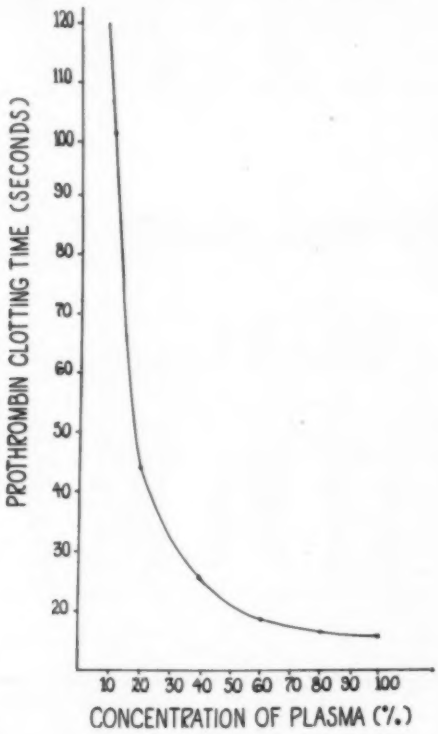

Fig. 6.

Fig. 5.—Prothrombin clotting times of serial dilutions of normal adult plasma, employing the Quick method and Thromboplastin No. 1 for the infants and adults in Group I. (Stable rabbit brain suspension prepared by Schieffelin & Company. Prothrombin clotting time of undiluted plasma was 13 seconds.)

Fig. 6.—Prothrombin clotting time of serial dilutions of normal adult plasma, employing the Quick method and Thromboplastin No. 2 for the infants and adults in Group II. (Stable rabbit brain suspension prepared by Schieffelin & Company. Prothrombin clotting time of undiluted plasma was 15.8 seconds.)

fants with an initial hypoprothrombinemia, the rate of decrease was more gradual from the onset of storage, although low levels of prothrombin concentration were reached sooner.

Of considerable practical importance is the effect of storage on adult plasma. It will be noted that during the first twenty-four hours the prothrombin concentration remained above 50 per cent in each subject. At the end of 3 days, the concentration still remained above 40 per cent. After 8 days of storage, the prothrombin concentration had dropped to levels ranging from 31 to 13 per cent. Thereafter, there was a slow but progressive decrease in concentration, so that after 33 days the prothrombin of all plasma specimens studied had decreased to concentrations below 5 per cent.

Among the adults of Group I, one plasma (No. 13) showed a rise in prothrombin concentration to 100 per cent on the second day, following a drop from an initial value of 99 to 80 per cent on the previous day. This apparent secondary rise was probably due to a technical error.

When, as with the series of normal adult plasmas in Group I, prothrombin determinations were carried out over a period of 33 days, the prothrombin clotting times became considerably prolonged, one specimen requiring as long as 450 seconds to clot; however, a recognizable clot was still formed in each case. No attempt was made to convert prothrombin clotting time values to percentage prothrombin concentration where the latter was below 5 per cent. It is of in-

TABLE III. PROTHROMBIN CLOTTING TIMES OF SERIAL DILUTIONS OF NORMAL ADULT PLASMA, EMPLOYING THE METHOD OF QUICK AND THROMBOPLASTIN NO. 1* (FOR THE INFANTS AND ADULTS IN GROUP I). PROTHROMBIN-FREE PLASMA WAS USED AS THE DILUENT

PLASMA CONCENTRATION (%)	PROTHROMBIN CLOTTING TIME (SECONDS)
100	13
80	14.6
60	16.6
40	20
20	32
10	57
5	99

*Stable rabbit brain suspension prepared by Schieffelin & Company.

TABLE IV. PROTHROMBIN CLOTTING TIMES OF SERIAL DILUTIONS OF NORMAL ADULT PLASMA, EMPLOYING THE METHOD OF QUICK AND THROMBOPLASTIN NO. 2* (FOR THE INFANTS AND ADULTS IN GROUP II). PROTHROMBIN-FREE PLASMA WAS USED AS THE DILUENT

PLASMA CONCENTRATION (%)	PROTHROMBIN CLOTTING TIME (SECONDS)
100	15.8
80	16.4
60	18.4
40	25.8
20	44
10	102.6
5	117

*Stable rabbit brain suspension prepared by Schieffelin & Company.

terest to note that in one adult plasma specimen there was no decrease in the initial prothrombin concentration of 100 per cent for twenty-four hours, despite storage.

As had been observed by previous investigators,[10-16] a relative hypoprothrombinemia with prothrombin concentrations of 17 to 64 per cent was found in the first forty-eight hours of life in the newborn infants of Group I who had not received vitamin K (Table I and Fig. 1). Prothrombin concentrations were generally higher (ranging from 56 to 100 per cent) in the newborn infants treated with vitamin K in Group II (Table II and Fig. 3), but these infants were somewhat older and ranged up to almost 6 days of age.

DISCUSSION

The results of the present study add to our information on the behavior of some blood-clotting factors and the relationship of these factors in newborn infants to those in adults.

The fact that the decrease in prothrombin concentration follows a hyperbolic curve when the plasma of the normal adult is stored is a most interesting phenomenon. This is of particular interest when it is noted that the familiar curve of prothrombin clotting times upon serial dilution of normal adult plasma is, likewise, hyperbolic.

The curve for the decrease in prothrombin concentration of plasma of the newborn infant when stored is similarly hyperbolic, regardless of the initial prothrombin concentration and irrespective of the administration of vitamin K.

These data strongly point to the probability that not only is prothrombin in the newborn infant similar to that of the normal adult, but also to the fact that additional clotting factors are, likewise, similar. This conclusion appears justifiable as a result of the fact that the method employed, namely, the method of Quick, measures prothrombin concentration together with its convertibility to thrombin. In view of recent knowledge, the factor of convertibility of prothrombin to thrombin must include the summation of not only prothrombin concentration and its convertibility to thrombin in the clotting mechanism, but also the additional accelerating and inhibiting factors in the plasma. Thus, the results of this investigation indicate that upon storage, the summation of all these factors (reacting individually, depending upon their concentrations, and interacting with each other), reacts similarly in the plasma of newborn infants and normal adults. A similarity of reaction upon serial dilution of plasmas of newborn infants and adults was described previously.[12] It would appear to follow, therefore, that not only is prothrombin in the newborn infant similar qualitatively and physiologically to that of the normal adult, but also that this similarity, likewise, exists with respect to other accelerator and inhibiting factors. This is probably true, regardless of the type of factors involved, whether these be the labile factor of Quick, the Ac-globulin of Ware and Seegers, the SPCA of Alexander and associates, Factor V of Owren, or other accelerating and inhibiting factors which further investigations may bring to light.

The graphic portrayal of the character of the decrease of plasma prothrombin on storage provides a valuable guide in the use of plasma as a source of pro-

thrombin. If a prothrombin concentration of from 10 to 20 per cent be accepted as a probable critical bleeding level, then plasma stored less than one week offers a ready source of prothrombin with an adequate level. However, because of its dilution on being infused into the vascular system, plasma is more effective as an antihemorrhagic agent when used in the fresh state. If fresh plasma is not available, somewhat older plasma may still be used effectively in an emergency. It would appear that plasma stored longer than one week would be of little value as an effective source of prothrombin.

CONCLUSIONS

1. When human plasma is stored at 10° to 20° C., the decrease in prothrombin concentration follows a hyperbolic curve.

2. The decrease in plasma prothrombin concentration upon storage follows the same pattern for the plasmas of newborn infants and of normal adults.

3. The decrease in plasma prothrombin concentration in newborn infants follows a hyperbolic curve, regardless of the presence or absence of hypoprothrombinemia, and regardless of whether or not vitamin K has been administered.

4. The similarity of reaction of plasma prothrombin of the normal adult and the newborn infant upon storage adds further evidence in support of the theory that prothrombin in the newborn infant is qualitatively and physiologically similar to that in the adult.

5. It is suggested that other accelerator and inhibiting factors in the mechanism of clotting are similar in the newborn infant and the normal adult.

6. Plasma is most effective as a ready source of prothrombin in the fresh state. However, when the latter is not available, somewhat older plasma may be used in an emergency to provide an appreciable amount of prothrombin.

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REFERENCES

1. Quick, A. J.: J. Lab. & Clin. Med. **33**: 819, 1948.
2. Quick, A. J.: Am. J. Physiol. **140**: 212, 1943.
3. Quick, A. J.: Am. J. Physiol. **151**: 63, 1947.
4. Seegers, W. H., Loomis, E. C., and Vandenbelt, J. M.: Arch. Biochem. **6**: 85, 1945.
5. Ware, A. G., and Guest, M. M.: Am. J. Physiol. **150**: 58, 1947.
6. Loomis, E. C., and Seegers, W. H.: Am. J. Physiol. **148**: 563, 1947.
7. Ware, A. G., Guest, M. M., and Seegers, W. H.: Science **106**: 41, 1947.
8. Ware, A. G., and Seegers W. H.: J. Biol. Chem. **172**: 699, 1948.
9. De Vries, A., Alexander, B., and Goldstein, R.: Blood **4**: 247, 1949.
10. Owren, P. A.: Lancet **1**: 446, 1947.
11. Quick, A. J.: Am. J. M. Sc. **214**: 272, 1947.
12. Kove, S., and Siegel, H.: J. PEDIAT. **18**: 770, 1941.
13. Rhoads, J. E., and Panzer, L. M.: J. A. M. A. **112**: 309, 1939.
14. Lord, J. W., Jr., and Pastore, J. B.: J. A. M. A. **112**: 309, 1939.
15. Warner, E. D., Brinkhaus, K. M., and Smith, H. P.: Am. J. Physiol. **114**: 667, 1936.
16. Ziegler, E. R., Osterberg, A. E., and Honig, M.: J. A. M. A. **114**: 134, 1940.
17. Fahey, J. L., Ware, A. G., and Seegers, W. H.: Surg., Gynec. & Obst. **88**: 870, 1949.
18. Quick A. J.: J. A. M. A. **110**: 1658, 1938.
19. Rosenfeld, R. E., and Tuft, H. S.: Am. J. Clin. Path. **17**: 495, 1947.

PROTHROMBIN IN THE NEWBORN INFANT

VI. Effect of Sulfadiazine on Prothrombin of the Newborn Infant

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IT HAS been suggested[1] that sulfonamides may cause a hypoprothrombinemia because of their inhibiting effect on the bacterial flora of the gastrointestinal tract with resultant interference in the normal production of vitamin K. The administration of sulfonamide drugs to rats for several weeks resulted in a decrease in prothrombin concentration.[2, 3] Contradictory reports[4-8] of possible increased bleeding in patients with carcinoma of the gastrointestinal tract who received succinylsulfathiazole, preoperatively and postoperatively, appear in the literature. Prothrombin studies are either not furnished, or data are too meager for drawing any conclusions on the influence of sulfonamide drugs upon the prothrombin of the blood. Bleeding may well have been due to other causes, such as the primary malignant condition. Wright and associates[9] found some increase in bleeding and clotting times in patients following the administration of Sulfathalidine. If sulfonamide drugs produce hypoprothrombinemia, the administration of sulfonamides in the neonatal period would be particularly hazardous, for at this time a hypoprothrombinemia is most common.[10-16] The latter is most marked in the first few days of life, and the prothrombin concentration gradually rises thereafter.[16] The low prothrombin level has been variously ascribed to inadequate storage of prothrombin in the fetus, inadequate secretion of bile, or local gastrointestinal conditions which may prevent adequate absorption of vitamin K, such as intestinal hypermotility and decreased absorptive ability of fat-soluble substances by the intestinal mucosa which may be present in the neonatal period.[17, 18] Other factors which may be contributory are deficiency in plasma globulins and transitory hydremia present during the first few days of life.[18] No relationship between the maternal dietary vitamin K intake and the prothrombin level in the newborn infant has been established.[16]

The subsequent rise in prothrombin concentration of the newborn infant is attributed to the introduction of bacteria with ingested food and resultant production of vitamin K by the bacterial flora in the gastrointestinal tract of the infant.[17]

Vitamin K from natural sources or one of the group of naphthoquinones having antihemorrhagic activity will prevent hypoprothrombinemia if administered to the infant.[19-23] The value of vitamin K or of the antihemorrhagic naphthoquinones in the prevention and treatment of hemorrhagic disease of the newborn infant is fairly well accepted.

It would appear, then, of considerable practical importance to know the effect of sulfonamides on the prothrombin concentration of newborn infants, because of the frequency of sulfonamide therapy.

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PURPOSE

The purpose of this investigation was to determine the effect of sulfadiazine in the usual therapeutic dosage upon the prothrombin of the newborn infant.

METHOD

Prothrombin determinations were done on the plasmas of six normal newborn infants, chosen at random, and ranging in age from 16 to 36 hours. Infants of this age group were chosen because the prothrombin concentration in the neonatal period is usually lowest during the first forty-eight hours.[16] After blood had been drawn, 0.13 Gm. sulfadiazine was administered orally to each infant every six hours (approximately 1 grain per pound per 24 hours); after seventy-two hours of sulfadiazine administration, blood was drawn from each infant for final prothrombin determinations. The infants had not received vitamin K, nor had the mothers received vitamin K before delivery.

The method of Quick[24] was used to determine the prothrombin clotting time. The thromboplastin employed was the stable rabbit brain suspension (Thromboplastin No. 1) described in our preceding study,* and yielded a prothrombin clotting time of 13 seconds for undiluted plasma of the normal adult. (All determinations were performed by the authors.) Prothrombin concentration, in terms of percentage of normal adult, was determined from a curve of the prothrombin clotting times of serial dilutions of normal adult plasma. This value is not a true quantitative measure of prothrombin concentration, but is really a summation of the factors of concentration in plasma and its convertibility to thrombin as compared to the normal adult plasma.

RESULTS

The prothrombin concentration of the six infants prior to receiving sulfadiazine varied from 17 to 64 per cent and, as expected, all exhibited varying

TABLE I. EFFECT OF SULFADIAZINE* UPON PROTHROMBIN CLOTTING TIME AND PROTHROMBIN CONCENTRATION OF 6 NORMAL NEWBORN INFANTS, LESS THAN 48 HOURS OLD, WITH VARYING DEGREES OF HYPOPROTHROMBINEMIA

	CASE 2		CASE 4		CASE 5		CASE 6		CASE 7		CASE 8	
INFANTS	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)	P.C.T. (SEC.)	P. CONC. (% N.A.)
Initial prothrombin determination	17.4	50	15.6	64	17	52	31	22	37	17	18.2	45
After 72 hours of sulfadiazine	16.2	58	14.6	70	13	100	15.6	64	15	66	13.8	86

*Two grains of sulfadiazine were administered orally to each infant every 6 hours for 72 hours.

P.C.T. = Prothrombin clotting time.
P.Conc. = Prothrombin concentration.
% N.A. = Percentage of normal adult concentration.
Sec. = Seconds.

*Prothrombin in the Newborn Infant V (p. 78).

degrees of hypoprothrombinemia in their plasma. Following seventy-two hours of oral sulfadiazine, the plasma prothrombin concentration of each infant rose to a varying degree from 6 to 49 per cent above the initial level prior to sulfadiazine administration, as shown in Table I and Fig. 1. It is interesting to note that the plasma of the infant with the most severe hypoprothrombinemia, namely 17 per cent, demonstrated the largest increase in prothrombin concentration with a final concentration of 66 per cent. Even plasma of the infant with an initial prothrombin concentration of 22 per cent showed a rise to 64 per cent, despite 3 days of oral sulfadiazine. In one infant, the prothrombin concentration rose to 100 per cent from an initial level of 52 per cent. A longer period of sulfadiazine administration was not possible because of the unavoidable short period of hospitalization of mothers and infants following delivery.

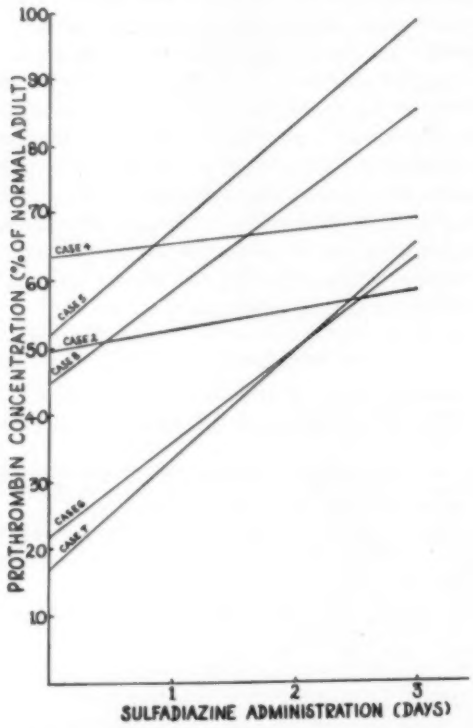

Fig. 1.—Effect of sulfadiazine upon plasma prothrombin concentration of six normal newborn infants, less than 48 hours of age. (Two grains of sulfadiazine were administered orally to each infant every 6 hours for 72 hours.)

Thus, sulfadiazine administered orally for 3 days not only failed to increase the degree of hypoprothrombinemia, but also failed to interfere with the usual rise in prothrombin concentration which takes place in the neonatal period from initial hypoprothrombinemic levels.

The group studied is admittedly small. However, because of the consistency of the results, it would appear that a short course of sulfadiazine in the usual therapeutic dose neither causes nor accentuates a pre-existing hypoprothrombinemia in the neonatal period, and adjunct vitamin K therapy is unnecessary. This conclusion does not militate against the advisability of administering vitamin K at birth routinely to overcome the hypoprothrombinemia which is usually present in the neonatal period.

CONCLUSIONS

1. The administration of sulfadiazine in the dosage of 1 grain per pound of body weight per 24 hours for 3 days to the newborn infant neither decreases the prothrombin concentration, nor does it prevent the expected rise in prothrombin concentration from the usual hypoprothrombinemic level present in the neonatal period.

2. The administration of sulfadiazine in the usual dosage for a short time to a newborn infant is not an indication for adjunct vitamin K therapy.

REFERENCES

1. Quick, A. J.: J. Lab. & Clin. Med. **3**: 468, 1946.
2. Black, S., Overman, R. S., Elvehjem, C. A., and Link, K. P.: J. Biol. Chem. **145**: 137, 1942.
3. Kornberg A., Daft, F. S., and Sebrell, W. H.: Pub. Health Rep. **59**: 832, 1944.
4. Kornberg, A., Daft, F. S., and Sebrell, W. H.: J. Biol. Chem. **155**: 193, 1944.
5. Allen, A. W.: Surgery **14**: 350, 1943.
6. Firor, W.: Ann. Surg. **115**: 829, 1942.
7. Sanders, G. B., and Halperin, P. H.: Surgery **20**: 82, 1946.
8. Poth, E. J.: Surgery **17**: 773, 1945.
9. Wright, L. T., Cole, F. R., and Hill, L. M.: Surg., Gynec. & Obst. **88**: 201, 1949.
10. Quick, A. J., and Grossman, A. M.: Proc. Soc. Exper. Biol. & Med. **40**: 647, 1939.
11. Quick, A. J., and Grossman, A. M.: Proc. Soc. Exper. Biol. & Med. **41**: 227, 1939.
12. Brinkhaus, K. M., Smith, H. P., and Warner, E. D.: Am. J. M. Sc. **193**: 475, 1937.
13. Waddell, W. W., and Guerry, D.: J. A. M. A. **112**: 2259, 1939.
14. Nygaard, K. K.: Acta. obst. et gynec. Scandinav. **19**: 361, 1939.
15. Hellman, L. M., and Shettles, L. B.: Bull. Johns Hopkins Hosp. **65**: 138, 1939.
16. Kove, S., and Siegel, H.: J. PEDIAT. **17**: 448, 1940.
17. Quick, A. J., and Grossman, A. M.: Proc. Soc. Exper. Biol. & Med. **40**: 647, 1939; Proc. Soc. Exper. Biol. & Med. **41**: 227, 1939.
18. Grossman, A. M.: J. PEDIAT. **16**: 239, 1940.
19. Poncher, H. G., and Kato, K.: J. A. M. A. **115**: 14, 1940.
20. Hellman, L. M., Moore, W. T., and Shettles, L. B.: Bull. Johns Hopkins Hosp. **66**: 379, 1940.
21. Lawson, R. B.: J. PEDIAT. **18**: 224, 1941.
22. Kove, S., and Siegel, H.: J. PEDIAT. **18**: 764, 1941.
23. Kove, S., and Siegel, H.: J. PEDIAT. **19**: 503, 1941.
24. Quick, A. J.: J. A. M. A. **110**: 1658, 1938.

Case Reports

CONGENITAL THROMBOCYTOPENIC PURPURA OF THE NEWBORN INFANT

Report of a Case

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THROMBOCYTOPENIC purpura occurs most frequently in children and young adults, but may appear in the first year of life or even occur at birth in full-term and premature infants.[1] McAlenney and Kristan[2] recently reviewed twenty-eight published reports embracing 36 cases of purpura in the newborn period. Their analysis included 30 of the previously reported cases, as well as 6 new cases. The appearance of cutaneous purpuric lesions at birth or shortly after was noted in 35 of the 36 analyzed cases. Melena occurred in 13 cases and hematuria in 2 of the cases reported. Splenomegaly was not present in any of the cases. The tourniquet test was positive in 10 out of 11 tested cases. A thrombocyte count under 100,000 per cubic millimeter occurred in 25 out of 29 cases, but did not signify a fatal prognosis. The average bleeding time was fourteen and one-half minutes and the average clotting time was seven minutes, but these values varied markedly and were often inconclusive. Anemia occurred only in association with severe hemorrhage.

The most constant and characteristic features of thrombocytopenic purpura in the newborn infants were: a generalized purpuric eruption, occasional melena, the absence of splenomegaly, usually a positive tourniquet test, and a reduction in blood thrombocytes. Although McAlenney and Kristan[2] feel that the disease is benign and self-limited in most instances, they nevertheless report a general mortality rate of 25 per cent in the 36 cases. In 19 of 36 mothers, purpura occurred during pregnancy and the infant mortality rate was 42 per cent, but it was only 6 per cent in the mothers without purpura. Seven mothers giving a history of purpura, but without occurrence during pregnancy, all had surviving infants with purpura.

The following case report is presented so that more data may be added to the relatively small number of cases of thrombocytopenic purpura in the newborn infant thus far reported.

CASE REPORT

B. B., a 28-year-old white woman, was admitted to the Beth-El Hospital in active labor, at term, on Oct. 7, 1949.

One previous pregnancy in 1946 had been normal and the child's development to the present was normal. The maternal past history revealed that she had always bruised easily but that during the present pregnancy there was a complete disappearance of this bruising tendency. During this pregnancy she enjoyed good health and experienced no bleeding, toxemia, rashes, or infections. There was no ingestion of drugs. No known allergies existed in the family.

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During labor there was no sedative administered. When there was 4 cm. dilatation of the cervix, continuous caudal analgesia was instituted with 1.5 per cent Metycaine.*

After a labor of five hours and twenty minutes, a male infant weighing 8 pounds, 2 ounces, was delivered from left occipitoanterior position by use of prophylactic low forceps.

The infant breathed immediately, appeared quite active, and had a lusty cry. No cutaneous lesions were observed at delivery. One and one-half hours after birth prominent petechial and a few purpuric spots were noted on the body. The extremities and trunk revealed the greatest number of these lesions but they were also found on the scalp, face, genitals, palms, and soles. There were several petechiae on the hard and soft palate. Several ecchymotic areas were noted on the face and there was a right parietal cephalhematoma. Heart and lungs were normal. Liver and spleen were not palpable. There was no oozing from the cord. No abnormal neurological signs were noted and the rest of the physical examination was within normal limits.

Laboratory studies at this time (see Table I) revealed 6,300,000 red blood cells and a hemoglobin concentration of 126 per cent. There were 12,000 white blood cells with a differential of 50 segmented neutrophiles, 6 stab neutrophiles, 2 eosinophiles, 3 monocytes, and 39 lymphocytes. No erythroblasts were found. Thombocytes were too few to be counted and on three successive blood smears an occasional giant platelet was seen which seemed to be in the process of breaking up. Clotting time was four minutes and the bleeding time one minute. The Rumpel-Leede test was strongly positive. Vitamin K, 2.4 mg. every four hours for six doses, and penicillin therapy were started at once.

During the next twenty-four hours the number of lesions increased. On the second day of life there was still a paucity of thrombocytes, clot retraction time was eight hours, prothrombin time was 85 per cent of normal, Mazzini was negative, and the blood was Rh negative, group O. The infant's general condition was excellent.

By the next day the thrombocyte count was 250,000 per cubic millimeter of blood and the rash began to fade. The tourniquet test was now negative. The stools were positive for occult blood. By discharge on the sixth day of life the hematologic studies were normal, there were no new purpuric lesions, and the old ones were fading away. The stools were soft and yellow with no occult blood. The infant was thriving and had regained his birth weight.

On the third day post partum a study of the mother's blood showed 370,000 thrombocytes, clot retraction time four hours, tourniquet test negative, Mazzini negative, Rh positive, group O, and prothrombin time was 100 per cent of normal.

COMMENT

The salient features in our case classifying it as one of congenital thrombocytopenic purpura are: (a) the mother gave a positive history of purpura; (b) the infant exhibited purpura one and one-half hours after birth; (c) three was a paucity of thrombocytes on direct count and smear; (d) there was a positive tourniquet test; (e) prolonged clot retraction time; (f) there was absence of splenomegaly; and (g) there was absence of any other etiological factors to account for the clinical picture. The infant made an uneventful recovery. This is in keeping with previous experience that the prognosis is excellent in those infants born of mothers who give a history of purpura but who exhibit no purpura during their pregnancy. Melena was not considered

*Received caudal analgesia (60 c.c. of Metycaine used) for one and three-quarter hours before birth of baby. This is a conduction type anesthesia and the medication remains extradural and is not absorbed into the mother's blood stream.

TABLE I. CHART OF BLOOD STUDIES

AGE	DAY OF BIRTH	2 DAYS	3 DAYS	4 DAYS	6 DAYS
Platelets (per cubic millimeter of blood)	A few large platelets—breaking up	A few large platelets—breaking up	250,000 per cubic millimeter of blood	250,000 per cubic millimeter of blood	300,000 per cubic millimeter of blood
Hemoglomin (%)	126		117		116
Red blood cells (per cubic millimeter)	6,300,000		5,290,000		5,600,000
White blood cells (per cubic millimeter)	12,000		18,000		6,400
White blood cells (differential count)	Segmented 50% Stab cells 6 % Eosinophiles 2% Monocytes 3% Lymphocytes 39%		Segmented 45% Stab cells 4 % Eosinophiles 12% Monocytes 8% Lymphocytes 30% Basophiles 1%		Segmented 42% Eosinophiles 6% Monocytes 1% Lymphocytes 51%
Bleeding time	1 minute				
Clotting time	4 minutes				
Prothrombin		85% of normal			
Mazzini		Negative			
Blood type		Group O Rh negative			
Tourniquet test	4+				
Clot retraction time		8 hours	Negative		Negative

to be present in our case despite a positive test for occult blood in meconium on the first and fourth days of life. A positive test for occult blood on the meconium stools of the first few days of life is not considered abnormal. Whether the source of occult blood is ingested maternal blood or the blood of the fetus itself is not known.[3] Therefore this test is hardly indicative of gastrointestinal tract bleeding.

In the differential diagnosis of this condition, sepsis, syphilis, erythroblastosis fetalis, hemorrhagic disease of the newborn infant, other hereditary hemorrhagic diatheses, and toxoplasmosis must be considered.

For therapy, the prophylactic use of penicillin to prevent sepsis and the administration of vitamin K to prevent hemorrhagic disease of the newborn infant so as not to add another bleeding tendency to one already present, is deemed advisable. Blood transfusions are of value in correcting a severe anemia secondary to hemorrhage. In addition, fresh whole blood will also supply platelets. Allen and co-workers[4] reported their clinical experience with the use of toludine blue in controlling the petechial hemorrhages in thrombocytopenia. This substance binds heparin and renders it biologically inactive. The dye is dissolved in isotonic sodium chloride and given in a dose of from 1 to 4 mg. per kilogram of body weight over a two-hour period. It affects capillary permeability and aids only in controlling petechiae. Bleeding is not entirely controlled unless blood transfusions are used to elevate the platelet count.

The thrombocyte count in newborn infants ranges from 140,000 to 290,000 per cubic millimeter of blood.[5] Other authors have found average platelet values of over 300,000 per cubic millimeter of blood at birth. The various differences depend upon the source of the blood and the method used for counting. A total platelet count well below the levels accepted as normal is salient for a diagnosis of thrombocytopenic purpura of the newborn infant.

SUMMARY

1. A case of thrombocytopenic purpura in a newborn infant is reported.
2. Present-day knowledge of this condition is briefly reviewed.
3. Emphasis is placed upon a generalized purpuric eruption, absence of splenomegaly, a usually positive tourniquet test, and a reduction in blood thrombocytes as diagnostic criteria.

REFERENCES

1. Wintrobe, M. M.: Clinical Hematology, Philadelphia, 1946, Lea & Febiger.
2. McAlenney, P. F., and Kristan, J. J.: Thrombopenic Purpura in the Newborn, Am. J. Dis. Child. **78**: 401, 1949.
3. Smith, C. A.: The Physiology of the Newborn Infant, Springfield, Ill., 1946, Charles C Thomas, Publisher.
4. Allen, J. G., Bogardus, G., Jacobson, L. O., and Spun, C. L.: Some Observations on Bleeding Tendency in Thrombocytopenic Purpura, Ann. Int. Med. **27**: 382, 1947.
5. Merritt, K. K., and Davidson, L. T.: Blood During the First Year of Life, Am. J. Dis. Child. **46**: 990, 1933.

SPONTANEOUS HEMORRHAGE FROM A HEMANGIOMA OF THE PONS

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SPONTANEOUS hemorrhage into the pons and medulla arising from a cavernous hemangioma of the pons is a rare condition, especially in a child, and few cases have been recorded in the English literature.[1-6,19] It is the purpose of this paper to report such an unusual case occurring in a 2-year-old child.

CASE REPORT

J. F., a 2-year-old girl, was first seen several hours after falling from her tricycle. It was not known whether she had accidentally hit the curbstone with her tricycle, or if she had suddenly collapsed. She, apparently, had cried immediately, and had not been unconscious.

The physical examination at this time was not abnormal. She was awake but irritable, and the deep and superficial reflexes were active and equal. The past and family histories were not unusual. She had never fainted or had convulsive seizures or postural unsteadiness, and there had never been any known visual or auditory symptoms. The physical examination of her younger sibling was normal except for a small hemangioma on one extremity.

Within three hours after her fall she vomited and became sleepy. The skull x-ray was negative for fracture, but she was hospitalized for observation. At this time, her pluse was 90 per minute and her blood pressure was 80/50. Her skin was cool and the temperature was 98.4° F. rectally. She was lethargic, but was very irritable when aroused. There was a small swelling in the occipital area, but no evidence of depression, and no bleeding was noted from the ears, nose, or mouth. The heart, lungs, and abdomen were not unusual. The reflexes were equal and hyperactive, and there was no evidence of muscular weakness. However, there was unsustained clonus of both ankles, and questionable Babinski reflexes.

For the first six hours after admission she remained drowsy and had a subnormal temperature. She could retain sips of water, however. She then began to have irregular sighing respirations and mucus rhonchi were heard bilaterally. Mucus tended to pool in the nasopharynx. Her blood pressure began to rise, 134/?, and the pulse rate rose to 124 per minute. Her pupils remained equal, but there was questionable decreased deep reflexes on the left. The temperature rose to 100.6° F. rectally. At this time, a surgeon felt intervention was not necessary.

By twelve hours after admission the child's condition had become critical; the fever was 105° F., pulse was 172 per minute, and she had Cheyne-Stokes type respirations. Her skin was mottled, and a little bloody mucus was noted in the pharynx. The left pupil seemed to be dilated, and reflexes seemed definitely decreased on the left. Her neck was a little rigid to forward flexion. She was given hypertonic glucose intravenously, continuous oxygen, and started on prophylactic penicillin. The temperature was artificially reduced. A spinal tap was not done.

The following morning (eighteen hours after admission) she had slightly less mucus in the nasopharynx, but the reflexes were unchanged. During lucid periods she would respond to questions. The blood count, at this time, was 94

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per cent hemoglobin, with 4,700,000 red blood cells per cubic millimeter. There were 8,700 white blood cells per cubic millimeter with 48 per cent neutrophiles and 52 per cent lymphocytes. She was given a small transfusion, plasma, and 75 c.c. of 20 per cent glucose. The temperature had fallen to 100.6° F. Improvement was transient, however, and twelve hours later she was irrational and cyanotic, and was having twitching movements of the left side of her body. Her left pupil was dilated, and the reflexes now appeared to be exaggerated on the left. The Babinski reflexes were negative.

On surgical consultation it was again felt that localization of signs was too indefinite for any procedures. Her fever once again started to rise, and respirations decreased to 12 per minute. Mucus pooling in the nasopharynx became a difficult problem despite aspiration and postural drainage. The swallowing and gag reflexes were absent. Further hypertonic fluids were given, but the fever continued to rise (106° F.), and the twitching movements became continuously convulsive in character. Her fever was uncontrollable, and she expired during a severe siezure, the temperature at that time being 107.2° F.

At post-mortem examination,* the child revealed no hemangiomas of the skin, and there was no evidence of laceration or contusion of the scalp, or hemorrhage into it. The bones of the skull were intact. The pertinent findings were limited to the brain. It was swollen and somewhat edematous. On removing it, a rather extensive accumulation of blood was seen in the region of the foramen magnum. This blood was mostly clotted, and completely encased the medulla oblongata. On section of the medulla, extensive hemorrhage was noted within its substance. This hemorrhage extended upwards into the pons. At one point the blood had perforated through the medulla, producing the aforementioned extravasation. Gross serial sections through the cerebral hemispheres and cerebellum showed no significant changes.

The histologic sections through the areas of hemorrhage in the pons and medulla showed extensive red blood cell extravasation. Macrophages containing old blood pigment were seen and there was considerable gliosis. Some of the sections showed clusters of dilated thin-walled vascular channels. These were closely packed together. They were lined by flattened endothelial cells and supported in a scant stroma. All of them were engorged with red blood cells. Adjacent to these clusters of dilated vessels were rather large areas of gliosis. The pathologic diagnosis was cavernous hemangioma of the pons with extensive hemorrhage into the pons and medulla oblongata.

DISCUSSION

Hemangiomas of the brain stem are infrequent, and this child appears to be among the youngest on record. Pineas[7] and Hawkins[2] each described one in an 18-year-old person. The earliest age of onset as reported by Bailey and Cushing,[8] and Cox and Trumble[9] was 17 years. Richardson[1] saw a patient who suffered apoplectiform attacks at the age of 7 years, and died fifteen years later of a spontaneous hemorrhage from an angiomatous vessel. He also mentioned the case of a 14-year-old child with a venous angioma of the upper midbrain.

In many of the recorded cases[10-12] of fatal hemorrhages into hemangiomas of the brain or spinal cord, there have been prolonged prodromal symptoms of a space-occupying lesion, and migrainous-type headaches have been reported.[2] In Rand's[13] series of cases of spinal cord hemangiomas there was a relatively long period when motor and/or sensory symptoms were slowly progressive, and it was unusual that this case had no preceding signs or symptoms since the lesion was in a peculiarly vital area. The case reported by Owen[3] was similar to this one in that the first neurological manifestations appeared to be coincident with the hemorrhage into the tumor.

*Dr. Max Appel performed the autopsy and pathologic examination.

Spontaneous hemorrhage or thrombosis of these angiomas is prone to happen, and many small recurrent asymptomatic hemorrhages may occur.[1] Hemorrhage is the common terminal episode.[1] Symptomatology depends on the location of the tumor. If rupture is into the subarachnoid space, signs of meningeal irritation may occur, while if the rupture is into the substance of the cord or brain stem, episodes of sensory or motor disturbance occur, which may clear as the clot absorbs. Recovery, however, is less likely if the hemorrhage involves the substance of the cord.[13]

In this case, diagnosis was made more difficult since there was the possibility of trauma being the cause of the patient's symptoms. Early, she presented the picture of cerebral concussion with shocklike symptoms, followed by a short lucid period which was in turn followed by signs of decompensation. The slow pulse became rapid, weak, and erratic, while the initially low blood pressure rose steadily. Respirations followed a similar course, and finally became Cheyne-Stokes in type.

With the appearance of a stiff neck, exaggerated deep reflexes, clonus, and bilateral Babinski reflexes and the loss of gag and swallowing reflexes, the picture changed, and suggested brain stem involvement. With these changes, and signs of meningeal irritation appearing, traumatic subarachnoidal hemorrhage or ruptured aneurysm seemed likely. She seemed to fall into Ehrenberg's[14] third classification of subarachnoid hemorrhage; namely, (3) an apoplectiform onset proceeding to coma, followed by meningeal signs. His other three classifications of subarachnoid hemorrhage are: (1) hemorrhage with only meningeal signs; (2) hemorrhage with an apoplectiform onset and subsequent recovery; and (4) hemorrhage with apoplectiform onset proceeding to, and death without the development of other signs.

Several of the symptoms or signs which sometime give a clue to diagnosis were absent in this case. Rand[13] states a nevus or hemangioma may occur in the dermatome supplied by the cord segment from which a pial hemangioma arises (Sturge-Weber syndrome[15]). Other helpful features such as hemangioma of the retina (Lindau-von Hippel syndrome[10]), or familial telangiectases (Goldstein[16]) were also absent. Cases like this without prodromata or definite localizing signs present a difficult problem of diagnosis, and even the terminal catastrophe can hardly be distinguished from ruptured intracranial aneurysm.[2] It is frequently impossible to make a diagnosis of the underlying cause of the dysfunction until it is exposed on the operating table.[20] However, when the syndrome of spontaneous subarachnoid hemorrhage is encountered, particularly if the victim is a child, the possibility of an arterial or venous angioma should be considered, and a cephalic bruit would be quite suggestive.[1]

Such intracranial accidents are best treated conservatively.[17] Hypertonic solutions have a distinct value in lowering the pressure. It would seem that there is considerable risk in carrying out a spinal tap in these cases.[1,13,17] Surgical explorations have been done, but in a majority of instances the hemangioma has not been interfered with. Ligation of the largest vessels has been attempted, but when death occurred later in these cases only remnants of tissue of the spinal cord were found at the site of operation.[19] Removal of the tumors is not usually feasible because of their vascularity.[20]

The origin of these hemangiomas has been ascribed to disturbances in embryologic development of the first anlage of the circulatory system, or to trauma.[6] In this case the defect was apparently congenital in origin. Most of these tumors consist of vascular spaces separated by glial tissue, and are almost always venous in nature. The majority of them have been found on the dorsal aspect of the cord, supposedly arising from the pial veins.[13] Some of the cases reported have been extrabulbar hemangiomas, but this hemangioma, like Owen's,[3] appeared to

be intrabulbar. Although it has been recognized that the floor of the fourth ventricle may be the site of telangiectases, solid vascular tumors, particularly intrabulbar ones, are quite unusual.[3]

SUMMARY AND CONCLUSIONS

1. Spontaneous hemorrhage into the pons and medulla arising from a cavernous hemangioma of the pons is a rare condition.

2. This paper reports such a case in a 2-year-old child.

3. Diagnosis is difficult when sudden hemorrhage is the first symptom. However, with the occurrence of spontaneous subarachnoid hemorrhage in a child, a ruptured angioma should be considered.

4. Associated nevi, skin or retinal hemangiomas, and familial telangiectases are helpful diagnostic aids.

5. Treatment is apparently conservative and symptomatic.

REFERENCES

1. Richardson, J. C., and Bagnall, A. W.: Canad. M. A. J. **43**: 111, 1940.
2. Hawkins, C. F., and Rewell, R. E.: Guy's Hosp. Rep. **95**: 88, 1946.
3. Owen, C. I., Webster, J. E., and Gurdjian, E. S.: J. Neuropath. & Exper. Neurol. **4**: 291, 1945.
4. Holt, L. M., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, 1938, D. Appleton-Century Co.
5. Ford, F.: Diseases of the Nervous System in Infancy, Childhood, and Adolescence, Springfield, Ill., 1946, Charles C Thomas, Publisher.
6. Schley, W.: Central. bl. f. allg. Path. u. path. anat. **41**: 337, 1928.
7. Pineas, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **110**: 281, 1927.
8. Bailey, P., and Cushing, H.: Tumors Arising from the Blood Vessels of the Brain, Springfield, Ill., 1928, Charles C Thomas, Publisher.
9. Cox, L. B., and Trumble, H. C.: M. J. Australia **2**: 308, 1939.
10. Lindau, A.: Proc. Roy. Soc. Med. **24**: 363, 1931.
11. Elkington, J.: Lancet **1**: 6, 1935.
12. Turner, O. A.: Arch. Path. **24**: 223, 1937.
13. Rand, C. W.: Arch. Neurol. & Psychiat. **18**: 755, 1927.
14. Ehrenberg: Hygiea **74**: 849, 1912.
15. Weber, F.: J. Neurol. & Psychiat. **3**: 134, 1922.
16. Goldstein, H.: Internat. Clin. **3**: 148, 1930.
17. Brenneman, J.: Practice of Pediatrics, vol. 4, Hagerstown, Md., 1944, W. F. Prior Company, Inc.
18. Krause, F.: Surgery of the Brain and Spinal Cord, vol. 3, New York, 1912, American Translation.
19. Buchanan, D., and Walker, A.: Am. J. Dis. Child. **61**: 928, 1941.
20. Craig, W., and Frugoni, P.: Proc. Staff Meet., Mayo Clin. **13**: 822, 1938.

CONGENITAL ABSENCE OF THE EXTERNAL GENITALS

(Persistent Primitive Cloaca)

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THE CASE to be reported is most unique in that complete absence of the external genitals is extremely rare. Such an anomaly is due to the failure of the primitive cloaca to subdivide. The cloacal division normally is completed during the seventh week of gestation.[1]

The primitive cloacal sac present showed no division for rectum, bladder, and urogenital sinus, nor was there any communication with the exterior. This common entodermal chamber received the fecal, urinary, and reproductive products. In higher mammals the cloaca is subdivided into a dorsal rectum, ventral bladder, and urogenital sinus. In such a manner two separate outlets are formed for fecal and urogenital discharge.

The infant reported by Choisy,[2] had no external genitals, but did show a protuberance between the thighs. This case differed from ours in that the pelvic organs were all present, a double uterus, Fallopian tubes, and ovaries.

The findings in our case in part resemble those seen in vertebrates below the placental mammals, in which the primitive cloaca retains a common entodermal chamber into which fecal, urinary, and reproductive products all pass and from which they are expelled to the outside. In the absence of the anus the child had no communication between the cloaca and the exterior. In addition to the above anomaly there was an absence of the kidneys and ureters. Agenesis of the kidneys frequently is associated with characteristic peculiar facies.[3] These children die soon after birth.[4]

CASE REPORT

The child's mother was a 20-year-old Mexican woman who had had a child three years previously. The father of the first child was not the father of the second. The present delivery was normal and spontaneous. Blood pressure during delivery was 130/90. The birth weight was 5 pounds, 1½ ounces, and the height was 17 inches. The child lived 24 hours. An x-ray taken of the entire child during life was interpreted by Dr. W. H. Yeider (Resident Radiologist) as follows: "No abnormalities of the cranial bones are noted. Dentition appears to be markedly retarded. There are abnormalities of fusion of the upper ribs on the left. The left thumb is present; however, there is no corresponding metacarpal bone. There are multiple abnormalities of fusion of the lumbar vertebral bodies. The sacral spine is completely abnormal with massive fusion of all of the bodies. There is marked soft tissue deformity of the left foot and only three toes noted on the right foot."

Impression.—Multiple congenital abnormalities of the skeletal system.

Since the sex of the child was not apparent it became a problem in selecting a name at the baptism. The difficulty was overcome by giving the child two names of both sexes: Jose Marie.

Necropsy Findings.—The body was that of a full-term Mexican child weighing 2,270 grams and 17 inches tall. The external genitals were absent and at the site the skin presented an area of deep pigmentation measuring 15 × 10 mm.

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The anus was imperforate, and in the region of the lumbar spine the skin presented a dimpled area. The feet were clubbed, and the right foot had only three toes. The left thumb was attached to the hand by a fibrous band. The right thumb was also frail but it had a bony attachment. Both knee joints felt rigid and fixed. The face showed peculiar changes (Fig. 1).

The nose was broad and flat. The chin was receded and pointed. The ears were large and set low. The distance between the eyes appeared widened. The heart weighed 16 grams (normal 17 grams), was dilated and the ductus arteriosus was widely patent. Each lung had only one lobe and it resembled the upper lobe. The left lung weighed 5 grams (normal 18 grams), and the right one weighed 11 grams (normal 27 grams).

Fig. 1. Fig. 2.

Fig. 1.—This photograph shows the absence of the external genitals, and the deformity of both feet and thumbs. The face shows a widening between the eyes, the chin is receded, the bridge of the nose is broadened and the ears are large and set low.

Fig. 2.—Note the imperforate anus, spina bifida occulta, and congenital clubbed feet.

The liver was enlarged weighing 130 grams (normal 78 grams). On sectioning the surface was dark purple-brown. The gall bladder and extrahepatic bile ducts were normal. The thymus weighed 10 grams; it was elongated, soft, and light purple-gray. The pancreas appeared normal. The stomach was filled with a thick mucoid material. The spleen weighed 6 grams; it appeared nodular, was firm, and the sectioned surfaces were deep purple-

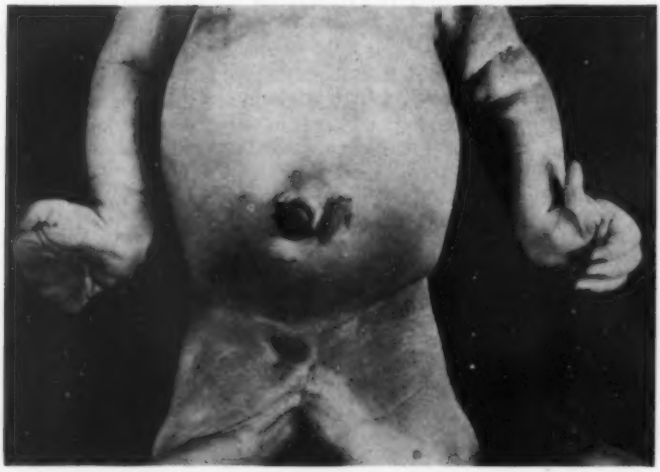

Fig. 3.—This photograph shows the absence of the external genitals and an area of pigmentation in the region of the symphysis pubis.
Note the fibrous attachment of the left thumb.

Fig. 4.—A photograph of the intestinal tract and pelvic organs. Ur, urachus; P.C., primitive cloaca sac; O, ovary; F, fallopian tube; U, poorly developed uterus; DC, dilated descending colon; S, collapsed sigmoid colon.

red. The kidneys and ureters were absent. The adrenals were of similar size and together weighed 8 grams (normal together 6 grams).

The small intestines appeared normal. The large bowel was dilated (Fig. 4), especially the descending portion which measured 26 mm. in diameter. The sigmoid was kinked and narrowed, measuring 8 mm. in diameter and it emptied into a sac (Fig. 4).

The sac (primitive cloaca) was attached anteriorly to the urachus and measured 40 mm. in anteroposterior diameter. At the inferior end it formed a knoblike protrusion (20 × 6 mm.) which subsequently proved to be the fundus of the uterus. Attached to the posterior aspect of the sac both ovaries and Fallopian tubes could be identified. The right ovary measured 14 × 2 mm. and was located posterior to the rectum as it entered the sac. The left ovary measured 11 × 1 mm.

The urinary bladder and urethra were absent.

Microscopic Examination.—Primitive Cloaca: A section made from the inferior aspect of the sac revealed the cavity to be lined by a thickened squamous epithelium resembling the vaginal mucosa, while the adjacent area of the sac was lined by a columnar type of epithelium, probably the mucosa of the urinary bladder. In the area where the rectum entered the cavity the lining of the sac resembled rectal mucosa. In another portion of the sac close to the knoblike projection (Fig. 4, *U*) the mucosa revealed proliferating glands with much mucus production suggesting cervical mucosa. The remaining portion of the area marked "U" was lined by a columnar epithelium resembling endometrium. The wall in the above described area contains smooth muscle and collections of spindle shaped cells suggesting endometrial stroma and the myometrium. Adherent to the serosa of the sac was an undifferentiated ovary rich in ova. At the periphery and close to the ovary sections revealed a Fallopian tube. Between the Fallopian tube and the ovary is a cordlike structure which probably was the ureter. It had a muscular wall and a narrow lumen lined by a layer of flattened epithelium.

Sections of the remaining organs showed nothing remarkable.

Anatomic Diagnosis.—There was: congenital absence of the external genitals; primitive cloaca composed of the urinary bladder, uterus, and vagina; agenesis of the kidneys with characteristic facies; imperforate anus; spina bifida occulta; malformation of the vertebral column; bilateral clubbed feet; and absence of both lower and right middle pulmonary lobes.

SUMMARY

The case reported illustrates an absence of the external genitals and the true sex of the child was determined at autopsy by the presence of two ovaries and Fallopian tubes.

In our case the primitive cloaca with its incomplete division is comparable to that seen in lower mammals or in the human embryo younger than seven weeks.

The absence of the kidneys have been noted to be associated with characteristic peculiar facies, so that in a group of newborn infants the absence of the kidneys could be predicted prior to necropsy by observing the facies.

REFERENCES

1. Arey, L. B.: Development Anatomy; ed. 5, Philadelphia, 1947, W. B. Saunders Company, pp. 278-281.
2. Choisy, R.: Absence of External Gental Organs and External Peritonitis; Gynéc. et Obstét. 13: 177, 1926.
3. Kirshbaum, J. D.: Facial Characteristics of an Infant Without Renal Function, California Med. 71: 148-149, 1949.
4. Potter, E. L.: Bilateral Renal Agenesis, J. PEDIAT. 29: 68-76, 1946.

MULTIPLE INTESTINAL OBSTRUCTION IN A NEWBORN INFANT WITH RECOVERY

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THE presence of this complicated intestinal condition in a newborn infant, the late onset of vomiting, the presumptive evidence of fetal peritonitis, and finally complete recovery after surgical interference prompts me to present this case report.

J. S., a male infant, was born April 7, 1949, at a local hospital. Birth weight was 5 pounds, 14 ounces. He was the product of a normal pregnancy and delivery. The mother had been well during pregnancy. The infant had not vomited during his hospital stay of 7 days; however, he took only about one-half ounce of milk formula per four-hour feeding. At age of 8 days (first day at home) he vomited the 6 A.M., 2 P.M., and 6 P.M. feedings, appeared acutely ill, and was immediately hospitalized. On admission he appeared lethargic, abdomen was distended, fontanel sunken, and cry was weak. There was visible peristalsis in isolated bowel loops over the abdomen. Rectal examination revealed scanty fecal material but no blood. X-ray picture of the abdomen revealed findings compatible with diagnosis of intestinal obstruction. (Fig. 1.) No areas of calcification were noted in the x-ray film. Temperature was 100° F., pulse 140, white blood count 8,000, polymorphonuclears 58, lymphocytes 36. Urine examination was negative.

Attempts at deflation of abdomen by introduction of a catheter into the duodenum was only partially successful. The usual treatment for shock was given including a blood transfusion, and after a few hours the infant was prepared for surgery.

Under drop ether anesthesia and oxygen, the abdomen was opened, and when the peritoneum was incised, a small amount (about 30 c.c.) of clear, straw-colored fluid escaped. The intestinal loops were greatly distended and there were many small, gray, nonfriable plaques covering the surface of these loops as well as the parietal peritoneum. They were described by the surgeon as non-recent organized exudate. On further examination there was a fairly thick band firmly attached to and encircling two loops of ileum in about the midileum region. (Fig. 3.) There was no evidence of volvulus or intussusception. When this band was severed, there was still much distention of the distal bowel and on further exploration, there was a similar band encircling the first portion of the ascending colon, approximately 4 or 5 inches from the ileocecal valve. This obstruction was much more complete. Immediately proximal to this band, the colon, for about 2 inches, was much smaller in size and its lumen comparatively small; its appearance was that of a partial atresia. (Fig. 4.) There were many enlarged lymph glands in this area. No perforation point of bowel could be found. This second band was also severed and after considerable discussion as to whether or not an anastomosis should be done in this apparently atresic area, it was decided to avoid such a procedure. This decision was fortunate, as, a few minutes later while the abdomen was being closed, the infant ceased breathing and resuscitative measures were necessary.

The postoperative course was stormy for forty-eight hours, but then progress was rapid and uneventful. At present the infant is 10 months old, weighs 24 pounds, and has no symptomatology referable to the gastrointestinal tract. Repeat x-ray of the gastrointestinal tract one month ago showed no abnormality. (Fig. 2.) *Culture of fluid from abdomen was negative.*

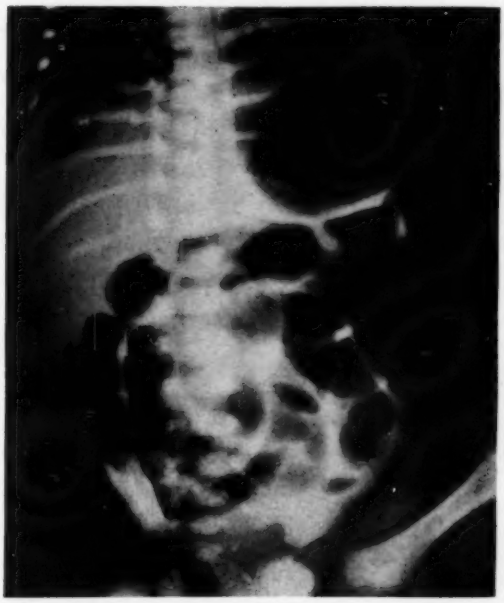

Fig. 1.—Preoperative x-ray film of abdomen showing distention of intestinal loops with gas: pattern compatible with that in intestinal obstruction.

Fig. 2.—Postoperative colon x-ray (barium enema) taken one month ago (at age of 9 months). No demonstrable obstruction. *B* points to area of spasm in transverse colon which filled well on fluoroscopy.

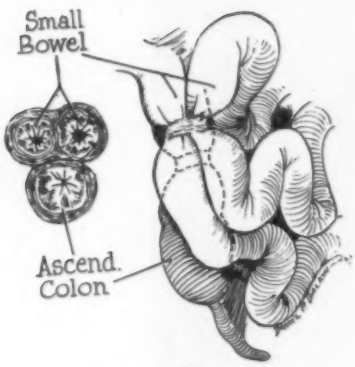

Fig. 3.

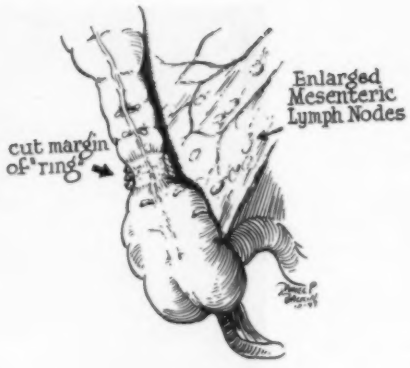

Fig. 4.

Fig. 3.—Schematic reconstruction of operative findings; view presented on opening abdomen.

Fig. 4.—View showing another area of obstruction by band in ascending colon; note area of apparent partial atresia.

DISCUSSION

The findings of fluid in the abdomen, the enlarged lymph glands, and the presence of organized exudate over the visceral as well as the parietal peritoneum, is suggestive of fetal peritonitis, most likely of the asceptic type which is often referred to as meconium peritonitis. The congenital bands may be either of maldevelopmental origin or secondary to fetal peritonitis. The asceptic peritonitis is a chemical peritonitis caused by entrance of meconium into the peritoneal cavity through a perforation of intestine occurring after the fifth month of fetal life.[1] The explanation usually given for the perforation is as follows: meconium stimulates peristalsis which, when working against an obstruction, causes a perforation of the intestines.[2] The obstruction may be in the form of atresia, bands, etc., or due to the meconium itself. Lacking intestinal enzyme secretion, the meconium becomes sticky and puttylike and adherent to bowel wall, which may obstruct lumen.[3] The perforation usually closes before birth.

SUMMARY

A case of multiple areas of intestinal obstruction, caused by congenital bands in an 8-day-old male infant is presented. One area of obstruction was in the midileum region and another more complete obstruction was in the ascending colon. The presence of some clear, straw-colored fluid in the abdomen, enlarged mesenteric lymph glands, and areas of organized exudate on the parietal and visceral peritoneum indicated that fetal peritonitis was present, possibly a meconium peritonitis. The late onset of vomiting (eighth day of life) can be explained by: a) incompleteness of the obstruction, b) low location of the obstruction, and c) the fact that the infant took very little food (one-half ounce of milk formula every four hours). Recovery after surgical interference was complete.

REFERENCES

1. Abt, I. A.: Fetal Peritonitis, M. Clin. North America **15**: 611-22, 1931.
2. Boikan, W. S.: Meconium Peritonitis, Arch. Path. **9**: 1164-83, 1930.
3. Landsteiner, K.: Darmverschluss durch eingedicktes Meconium. Pankreatitis, Centralbl. f. allg. Path. u. path. Anat. **16**: 903, 1905.

Medical Progress

NEWER KNOWLEDGE ON THE PATHOGENESIS OF POLIOMYELITIS

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INTRODUCTION

BEGINNING with the early studies of experimental poliomyelitis much attention has been focussed on the mechanism of infection which determines entrance of the virus into the body and the mode of its subsequent dissemination. The subject is of more than academic interest, since any rational approach toward prophylactic or therapeutic control of the disease depends, in essence, on a proper understanding of these fundamental principles. Unfortunately, the pathogenesis of poliomyelitis is a highly complex problem involving properties of the virus and of the host in intricate relationship, and a systematic presentation of its many ramifications would transcend the scope of this review. It is possible, however, and perhaps profitable, to select for critical examination at this time one single aspect which lends itself to experimental analysis. We are referring to the question of whether Heine-Medin disease—as an epidemiological and clinical entity—is primarily an affection of the central nervous system or a systemic infectious disease which culminates secondarily in the involvement of nervous tissues. From a pathologic standpoint the subject resolves itself into a discussion of whether the pathognomonic lesion in the anterior horn represents an obligate and incipient manifestation of the morbid process or an accidental and terminal complication. From a virological viewpoint, it will be necessary to weigh the evidence as to whether the etiological agent is an exquisite neurotropic virus or, possibly, a pantropic virus endowed with the ability to form a neurotropic variant. Efforts to delve into the underlying basic principles through the study of human autopsy material are handicapped by distinct limitations. More promising is the approach through the use of experimental methods which permit control over many of the variable factors. It is proposed in this paper to review briefly a number of recent experimental observations which bear on the subject. These contributions are slowly beginning to crystallize and fit into a picture of the mechanism of infection that appears to be in reasonable agreement with our present clinical and epidemiological knowledge of the human disease. The field is still an obscure one in which information is seldom precise, more often ambiguous or conflicting, and new data are being added faster than they can be absorbed. Hence, any interpretation of such data must, of necessity, be provisional and should remain open to revision as the need for reorientation may arise.

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GENERAL CONSIDERATIONS

When poliomyelitis was first recognized as an infectious entity, causing the occurrence of spinal paralysis in epidemic form, the disease was named by borrowing from the pathologist the term that accurately describes the nature and seat of the lesion at the autopsy table. Because paralytic cases were comparatively rare, even at the height of epidemics, the disease appeared to be due to an agent possessed with little infectivity, and epidemiological investigation could seldom establish physical contact between two cases of paralysis. Yet, earlier clinical observers had already pointed out repeatedly that poliomyelitic infection might not necessarily be restricted to the central nervous system. In fact, to some the malady gave the impression of a systemic disease with initial lesions localized in peripheral structures, such as the gastrointestinal tract and the lymphatic apparatus.[1, 2, 3] This opinion (even though from it sprang our present concept of the epidemiology of poliomyelitis) fell short of formal acceptance for a long time, chiefly because extraneural lesions and extraneural dissemination of the virus, could not be duplicated in rhesus monkeys. However, as finer diagnostic criteria were developed and applied to a systematic study of cases and contacts, it became increasingly more evident that many individuals in an epidemic area were suffering from minor febrile illnesses, often without any objective neurological signs.[4] The sum total of these observations carried sufficient conviction to lead ultimately to a clinical and statistical recognition of what has been called *poliomyelitis sine poliomyelitide*, i.e., the nonparalytic or abortive type of the disease. Proof of the infectious state was furnished by detecting a wide dissemination of the virus in the stools and pharyngeal secretions in abortive cases and by charting the characteristic appearance of neutralizing antibodies in their sera.[5] Experimental verification of the new concept, however, was not forthcoming until monkeys other than Macacus rhesus could be successfully infected by feeding the virus.[6] With this fact established, it was soon discovered that in the cynomolgus (Java) monkey, for instance, the infectious agent is recoverable not only from the stools and walls of the pharynx but also from the abdominal viscera;[7] moreover, oral infection of chimpanzees reproduced subclinical poliomyelitis with prolonged fecal excretion of the virus.[8] In other words, by abandoning the rhesus monkey as the animal of choice, concrete experimental evidence was eventually adduced to show that the virus caused a much broader tissue reaction, corresponding more closely to what had already been suspected from clinical studies of the human disease.

It is now generally known that nonparalytic cases far outnumber the paralytic cases, both as a nosological entity and as a source of infection in the epidemiological pattern. In fact, nonparalytic poliomyelitis is currently regarded as the typical and most common response of man to the virus.[9] It follows that central nervous system involvement, with permanent injury to the anterior horn, should be rated as an accidental feature of the disease, comparable in its biological significance to measles, mumps, or herpetic encephalomyelitis. What has therefore been named acute anterior poliomyelitis for over fifty years in the history of Heine-Medin disease, emerges today as one of the most widespread, highly communicable, generalized infections of childhood, a process which

in nearly 90 per cent of the cases remains limited to peripheral structures and exhibits marked tendencies toward complete recovery. The real clinical syndrome of this condition is as yet poorly defined and so are a variety of diffuse extraneural lesions or functional disorders.[10] It is important, however, to emphasize that without this general reorientation in the field, no objective evaluation would be possible of the gradually accumulating store of knowledge concerning the visceral pathology and symtomatology of this disease.

EXPERIMENTAL FACTS

We shall now proceed with a more detailed discussion of the experimental evidence which exists to show that the virus is capable of (a) inducing lesions in the peripheral neuromuscular apparatus, and (b) of multiplying in tissues outside the central nervous system. The data are still fragmentary and are drawn partly from observations with human subjects and partly from results obtained in rodents infected with strains of mouse-adapted or murine poliomyelitis virus. As will be shown later, however, the two sets of data are in essential agreement with each other.

A. Observations Derived from Experimentation with Human Beings.—

Lesions at the myoneural junction: As early as 1943 Carey[11] examined the histologic changes that occur during the early phases of the disease in human beings. In studying reports of three patients who had died of fulminating bulbar poliomyelitis, the conclusion was reached that the paralytic process originated at the myoneural junction with a rapid destruction of motor end plates, thence proceeding by centripetal extension in the axons of many nerve trees. Anatomic denervation of the respiratory muscles (diaphragm, intercostals, etc.) was held to be the result of pathologic changes going on during the incubation period, prior to the appearance of clinical symptoms. Similar motor end plate lesions were subsequently described by Sanz Ibanez[12] in biopsy samples obtained from acutely paralyzed patients. The crucial point in this type of investigation is, of course, first, the difficulty of agreeing on what constitutes pathologic alteration in ameboid structures like motor end plates; secondly, the uncertainty as to whether such changes are primary or secondary and whether they truly represent the point of initial attack of the virus. As one looks for changes in the muscle fibers themselves, surprisingly little accurate information is available if one eliminates the atrophic changes, which occur in cases of long standing,[13] and considers only the pathology during the acute stage of paralysis.[14] There is on record a well authenticated case of fatal poliomyelitis of the ascending Landry type in which widespread lesions were present not only in the central nervous system but also in the heart and in the muscles of respiration (diaphragm, intercostals, pectoral muscle). The latter consisted of muscle fiber degeneration and inflammatory infiltration with fibroblasts and lymphocytes.[15] Another case of fatal bulbar poliomyelitis in which extensive muscle lesions were seen (similar to those observed in suckling mice paralyzed by Coxsackie virus) is said to have occurred at the Buffalo General Hospital.[16] On the other hand, Clawson[17] found no myositic lesions in muscle samples obtained from

22 patients with acute fatal poliomyelitis which could not be duplicated by the examination of muscle samples from 292 individuals dead of diseases other than poliomyelitis. In fact, the numerical incidence of myositis was actually lower in poliomyelitis than in the majority of other diseases. During the 1949 epidemic we had an opportunity to examine biopsy samples obtained during the acute stage from the paralyzed muscles of 13 patients with nonfatal poliomyelitis. None of these specimens showed any significant pathologic changes. However, from one muscle biopsy in this series we were able to isolate a virus which paralyzed cynomolgus monkeys with the production of classical anterior horn lesions and well-defined myocardial lesions in the heart muscle.[18] The proved presence of the virus in the paralyzed limb pleads in favor of assuming a peripheral inception of the infectious process in this particular case.

It is not within our province to discuss the results obtained in testing neuromuscular functions in paralyzed muscles by electrophysiologic methods for evidence concerning the presence or absence of peripheral alterations. The available data have recently been reviewed by Buchthal[19] who concludes "that unquestionable signs of peripheral motor alterations, apart from atrophy, do exist."

Myocarditis: While little can be said as yet concerning the presence of lesions in the skeletal muscle of poliomyelitis patients, a substantial body of data has been collected in recent years which points to severe involvement of the heart muscle in the human disease. For a long time, of course, clinical experience had already recognized tachycardia as a symptom in many poliomyelitis patients. Following some scattered observations by earlier workers, Saphir and Wile,[20] in 1942, first drew attention to the frequent occurrence of interstitial myocarditis in fatal cases. Rapid confirmation of these findings came with subsequent publications by Peale and Lucchesi,[21] Dolgopol and Cragan,[22] and Ludden and Edwards.[23] The characteristic lesion has been described as a focal necrosis of individual muscle fibers with varying degrees of inflammatory cell response in the affected areas.[24] The unusually high incidence of acute myocarditis in severe cases of poliomyelitis—somewhere between 30 and 40 per cent in the over-all statistics of fatal cases (Table I)—is also reflected in cardiac studies during the lifetime of poliomyelitis patients.[25] A comprehensive report, published in 1947 by the Philadelphia group of workers,[26] gives a description of the electrocardiographic findings in 226 acute cases of nonfatal poliomyelitis. Abnormalities appeared in 32 cases, with a significant correlation between the frequency of their occurrence and the severity of the disease. It has been pointed out that myocarditis may be found with many other infectious diseases, including some of virus origin. Hence, the assumption that cardiovascular lesions in poliomyelitis are caused specifically by the poliomyelitis virus would be greatly strengthened if it were possible to isolate the virus from the heart muscle and to reproduce the condition in experimental animals. In 1949 we succeeded in isolating the virus from the heart, as well as from the cord, of two fatal cases of bulbar poliomyelitis by transfer to cynomolgus monkeys. Both heart and cord strains produced paralysis with classical anterior horn lesions,

but associated with this was the occurrence of definite myocardial involvement in several of the subpassages.[27] This observation would tend to place the occurrence of myocarditis not so much with the disease, as a chance phenomenon, but rather with the etiological agent, as a specific characteristic of the strain. In other words, the myocarditis-producing ability of poliomyelitis virus is comparable to the ability of diphtheria toxin, for instance, to cause myocardial involvement. These data, therefore, support the same conclusion which Ludden and Edwards[23] had previously reached, namely, "that the lesions in the heart muscle cannot be satisfactorily explained without ascribing them to the virus of poliomyelitis."

TABLE I.

A. Myocarditis in Fatal Human Poliomyelitis

AUTHOR	YEAR	TOTAL CASES	MYOCARDITIS	PER CENT
Saphir and Wile	1942	7	6	85
Peale and Lucchesi	1943	9	7	77
Gefter and associates	1947	11	6	54
Dolgopol and Cragan	1948	87	16	18
Ludden and Edwards	1948	35	14	40
Total	1942-48	149	49	32

B. Electrocardiographic Abnormalities in Nonfatal Human Poliomyelitis

AUTHOR	YEAR	TOTAL CASES	EKG ABNORMALITIES	PER CENT
Battro and associates	1943	20 (acute)	4	20
Battro and associates	1943	18 (chronic)	0	--
Gefter and associates	1947	226 (acute)	32	14
Firpi and associates	1949	44 (acute)	10	23
Total	1943-49	290 (acute)	46	16

It is too early to assay properly the significance of myocardial involvement in the over-all clinical picture of poliomyelitis. While the heart is, perhaps, the most vulnerable muscular organ, it is also made up of very resilient tissue. This means that the heart muscle may be expected to register early damage, but is also capable of prompt repair. Since the frequency of myocardial involvement seems to be directly proportional to the severity of the disease, it is not impossible that the fatal outcome in so-called bulbar cases may, at times, be determined more directly by the extent of myocardial damage than by lesions in the respiratory centers of the brain stem. For many of such patients eventually die in the respirator, despite passively maintained respiration. It will also be necessary, on the other hand, to examine carefully the occasional patients with "cryptic" myocarditis of unknown etiology (who show no obvious signs of paralysis), for the possible presence of poliomyelitis virus, especially when such cases occur at times of epidemics. In this connection, we should like to mention the case of a 15-year-old boy who was admitted to the Presbyterian Hospital in the midst of the 1949 epidemic. The patient complained of acute respiratory distress, but there were no signs of paralysis. The electrocardiogram suggested auricular enlargement. Despite oxygen administration the fever rose to 102.4° F. and death occurred ten hours later with symptoms of cardiovascular collapse. The autopsy showed no lesions in the central nervous system, but

there was present an incipient patchy pneumonia and a severe myocarditis with widespread hemorrhages and extensive muscle fiber necroses throughout the heart (Fig. 1). Unfortunately, no material was saved for virus studies and the final diagnosis, therefore, had to remain uncertain.

Fig. 1.—Acute myocarditis of unknown etiology in a human being. The patient was admitted to Presbyterian Hospital, New York City, August, 1949.

Viremia: The role of the blood stream as a possible vehicle for the transport of virus in human poliomyelitic infection has as yet not been thoroughly studied. Earlier investigations are based on limited data or have operated with inadequate experimental methods. In 1946 the problem was reinvestigated by Ward and associates[28] who tested nineteen pooled samples and fifty-six individual samples of blood, representing a total of 111 patients. However, of the 111 patients in this series, only 20 were examined on the first day of illness and of these only 2 were of the paralytic type. Poliomyelitis virus was detected in the blood in only one abortive case, not more than six hours after the onset of symptoms. The authors interpreted their findings as suggesting that the presence of poliomyelitis virus in the human blood stream is not a common event. However, the data do not exclude a possibility that in poliomyelitis, as in yellow fever, virus

may circulate only during the incubation period, or at best during the earliest phases of the disease, and that fixation by susceptible tissues may remove the agent rapidly from the blood stream as clinical symptoms set in. Further work is, therefore, needed to determine whether viremia is or is not a characteristic feature of the extraneural stage of poliomyelitis in man.

B. Observations Derived from Experimentation with Laboratory Strains of Virus.—

1. Strains of murine poliomyelitis virus: Quite in contrast to the sparse data collected so far from direct observations in man, a wealth of information is available from the study of the experimental disease in rodents infected with mouse-adapted virus. Rodent poliomyelitis, as a model of infection, has many advantages to offer over simian poliomyelitis, particularly since some murine strains produce the experimental disease by natural routes of infection. The various murine strains are derived either directly from human material (cord, blood, feces) or from monkeys originally infected with such material. Their transfer to mice, with notable exceptions, has usually been accomplished by intermediary passage through cotton rats or hamsters.

Some of these strains, especially the Lansing virus,[29] have found willing acceptance among scientific workers as agents representing the true characteristics of human virus. Others, like MM virus[30] and Columbia SK virus,[31] while similar in many respects, are, as yet, not definitely classified because of certain divergent properties. Following its original adaptation to mice at Columbia University (1940), the rodent-pathogenicity of SK virus was confirmed in two other laboratories. To add to the confusion, however, the resulting murine strains were either similar to Col. SK virus (Toomey, 1947[32]) or resembled the Lansing virus (Melnick and Ward, 1945[33]); the latter strain has since been designated as Yale SK (Y-SK) virus. Two additional neurotropic viruses which also produce the picture of experimental poliomyelitis in rodents, i.e., so-called encephalomyocarditis virus (EMC),[34] and Mengo encephalomyelitis virus,[35] were subsequently isolated from obscure sources. These two viruses appear biologically and antigenically so closely related to Col. SK and MM viruses that the four viruses are currently referred to as the Col. SK-MM-EMC-Mengo group of viruses.[36, 37] Finally, a number of strains were recently isolated in infant mice from the stools in paralyzed or nonparalyzed cases which had been diagnosed and reported as poliomyelitis.[38, 39] Because of their unusual properties these viruses are currently suspected to be the causative agents of another disease, resembling poliomyelitis in many respects but distinct from it, and possibly bridging the gap between poliomyelitis and epidemic myalgia. They are therefore, at present, classified under a separate name, i.e., Coxsackie group.

The various strains listed may be conveniently placed into three separate subgroups, i.e., Lansing group, Col. SK-MM-EMC-Mengo group, and Coxsackie group. There are good reasons for believing that the strains of all three subgroups are human pathogenic and are capable of producing poliomyelitis or poliomyelitis-like disease in man. All have been used, from time to time, as models of experimental poliomyelitic infection. The three groups differ among

themselves in serologic and certain biologic properties but share the basic characteristics of human poliomyelitis virus, to wit: particle size of 8 to 15 mμ, neutralizability by human convalescent poliomyelitis serum, no immunologic relationship with strains of Theiler's spontaneous mouse encephalomyelitis virus (OT, GDVII, FA), ability to produce in monkeys (rhesus or cynomolgus) flaccid paralysis with typical poliomyelitic cord lesions or subclinical infection with prolonged fecal excretion of virus, and ability to paralyze rodents with or without central and/or peripheral lesions. In view of these facts, it seems a reasonable assumption that all three subgroups should be regarded as members of a broad group of human poliomyelitis virus, forming a system which exhibits a series of successive gradations in virulence and affinity for neural and extraneural tissues. The problem is more fully discussed in another article.[40]

2. Growth requirements of the virus in vitro and in vivo: In studying the selective tissue affinities of a virus there is no more objective test than to determine the ability of the agent to multiply on different types of cells. This approach is a direct counterpart to the more refined experimental procedures which are generally employed for determining the growth requirements and metabolic activities of bacterial microorganisms.

When Col. SK virus was first grown successfully in minced embryonic mouse tissue culture medium, it was realized that a certain basic level of multiplication could be maintained in the absence of central nervous tissue. This was conclusively shown by transplanting the virus, which had previously been propagated on mouse embryonic brain, into culture media containing whole mouse embryo from which the brain and cord had been removed.[41] Similar observations were subsequently made by Enright and Schultz,[42] who studied propagation of Col. SK and MM viruses in embryonated eggs. Inoculation with abdominal chick viscera yielded about the same virus growth as inoculation with the heads and necks only. More recently the propagation in vitro of the Lansing strain in human embryonic tissue was reported.[43] Again, multiplication of the same order occurred not only on brain, but also on intestine and muscle tissue. In later experiments multiplication was also obtained on completely differentiated nonnervous tissue fragments, such as human foreskin. Moreover, the Brunhilde strain (immunologically distinct from the Lansing strain and nonadaptable to rodents) could likewise be maintained in active multiplication in skin-muscle cultures of human embryos.[44] The experimental evidence, therefore, is surprisingly unequivocal in showing that, under controlled conditions of growth, several strains of human poliomyelitis virus, irrespective of their degree of neurotropism or viscerotropism, will multiply in the absence of nervous tissue. Thus, these data permit of only one conclusion: namely, that poliomyelitis virus is not an exquisite neurotropic virus but a pantotropic agent capable of thriving vicariously on nervous as well as on nonnervous tissue elements.

Another approch to the same problem is possible by studying the fate of the virus, i.e., its accumulation and distribution in various tissues, following injection into susceptible animals. Beginning with the early experiments, it was already apparent that intracerebral infection with the different murine

strains serves to accumulate high viral concentrations in the central nervous system, suggesting local growth. Virus levels in the cord could be shown to exceed those of the brain for practically all strains tested. The frequent occurrence of unilateral lesions and of asymmetrical paralytic symptoms confirmed the fact that poliomyelitis virus, unlike encephalitis virus, once in the central nervous system, follows strictly nervous pathways. Recovery of the virus from extraneural tissues (blood, spleen, etc.), rare with the "low" strains (Lansing group) and common with the "high" strains (Col. SK group), has been tentatively interpreted as a "spill-over" effect. Fecal excretion, so highly characteristic of infection with "high" strains, received no further detailed study and its precise mechanism remained unexplained. Because of the unnatural portal of entry, these experiments contribute little or nothing to our knowledge of the potential tissue affinities of the virus beyond demonstrating that the agent, once it is introduced into and contacts nervous tissue, has the properties of a neurotropic, even neuronotropic, agent. New light was shed on this problem when these experiments were repeated with murine virus, permitting peripheral infection. Thus, Sanz Ibanez[45] was the first to demonstrate the actual presence of the virus in the paralyzed muscle of guinea pigs following intraperitoneal infection with Col. SK virus. Subsequent experiments showed that in young guinea pigs which had been infected intramuscularly with MM virus, the initial paralytic involvement occurred concordantly with the chosen portal of entry in 76.7 per cent of the subjects.[46] Localization of paralysis, therefore, which is entirely haphazard following inoculation by any other route, became predictable —as in local tetanus—with the choice of a predetermined muscular site of injection. Local multiplication and local attack of the virus in the infected muscle appeared to be a logical premise. In 1948 Evans and Chambers[47] carried out a careful analysis of the kinetics involved in the distribution of MM virus between extraneural and neural tissues by plotting virus concentrations in different tissues against time intervals. Their data brought conclusive proof that, following injection into the foot pad of hamsters, the virus increased in amount in the local tissues, followed in turn by viral increases in the blood and viscera, and that the virus appeared in the central nervous system only after a critical threshold concentration had been reached extraneurally. The described chronological sequence of events leaves little doubt that invasion of the central nervous system, under the conditions of these tests, was terminal. A similar mode of virus multiplication and dissemination presumably also controls the mechanism of infection with Coxsackie virus, since larger amounts of virus are found more frequently in the paralyzed muscles than in the brain.[48, 49]

The results obtained from in vitro and in vivo tests are in good agreement with each other. The data add up to one conclusion, namely, that certain strains of poliomyelitis virus possess, in addition to their characteristic neurotropic properties, well-developed viscerotropic (myotropic) qualities which enable them to propagate actively in nonneural tissue (especially muscle) prior to invasion of the central nervous system. In this respect, these viruses are not distinct from certain other neurotropic viruses, such as B virus or equine encephalomyelitis virus, which share the same properties. There is this difference, how-

ever, between the poliomyelitis group and the encephalitogenic group of viruses, that the former, in their neurotropic qualities, exhibit marked preference for the lower motor neuron, particularly the anterior horn, whereas the latter have a tendency to spread indiscriminately across blood vessels throughout the axis of the entire central nervous system. The data are not sufficiently clear to evaluate properly the function of the bloodstream in experimental poliomyelitic infection. While viremia probably exists during the extraneural stage, there is no compelling evidence to assume that the virus, once in the central nervous system, follows any other route than nervous pathways.

3. Lesions at the myoneural junction: Lesions in the peripheral motor neuron may appear as alterations either in peripheral motor nerves, or in their terminal motor end plates, or in the attached muscle fibril itself. In any event, pathologic changes will interfere with transmission or proper utilization of the nerve impulse. It is conceivable that functional (chemical) derangement, without demonstrable structural changes, may also be part of the picture in transient paralytic involvement, leading to hypertonicity (so-called spasm) in some muscle groups and to hypotonicity (myasthenia gravislike myopathic syndrome) in others. Hence the rationale for the clinical trial of various cholinesterase-inhibitors, on the one hand, and of curare-induced blockade, on the other, in poliomyelitis patients during the acute stage of the disease.

Numerous reports may be found in the literature drawing attention to a possible involvement of peripheral nerves in the paralyzed muscle of experimentally infected animals. However, since most of the older experiments were carried out in intracerebrally infected animals, they fail to provide any definite clues as to whether the observed peripheral changes were primary or secondary. In brief, destruction of ganglion cells in the anterior horn may have occurred first and damage to nerve fibers later.[49, 50, 51] In 1936 Toomey and Weaver[52] initiated a new approach to the problem by studying, between crossed Nicol prisms, the somatic nerves (coming from the lumbar and sacral segments) of monkeys which had been infected by injecting the virus (RMV strain) into the subserosal layer of intestinal loops. Within twenty-four hours these nerves exhibited obvious changes in their fibers, i.e., extensive vacuolization and disintegration of fasciculi fibers; in forty-eight hours there was almost complete destruction of individual nerve fibers in some animals. No comparable changes were found in monkeys which had received the virus by the intracerebral route. In peripheral infection, therefore, nerve involvement apparently preceded cell destruction in the anterior horn of the cord and produced early symptoms. This line of experimentation was later continued by Carey[53] who studied histologically more than 2,000 teased preparations from different muscles of monkeys injected intracerebrally with the Lansing strain. Coincident with and shortly after paralysis the following morphologic changes were observed: (1) disappearance of many motor end plates resulting in denervation at the myoneural junction, (2) appearance of masses of "inclusion bodies" (10-85 μ long) in the muscle fibers near the zone of disintegrating innervations, and (3) degeneration beginning in the motor end plates and apparently proceeding in a centripetal direction along the axis-cylinders of many motor nerves. Motor end plate changes were

subsequently described by Sanz Ibanez[45] in the paralyzed muscles of mice and guinea pigs infected peripherally with Col. SK virus. Again, the changes were similar in that the nerve fibrils in the affected muscles suffered either a complete ablation of motor end plates or these structures were extensively and severely distorted.

On may conclude from these experiments that poliomyelitic infection is associated with fairly characteristic lesions in the peripheral nervous system, especially at the myoneural synapsis, and there is some evidence to suggest that early peripheral lesions may appear before central lesions in the spinal cord are fully established. It is not advisable to go beyond this statement, at present, and the problem deserves further close study. Doubtless, physiologic function tests will play an important part in helping to clarify the issue. Attempts to demonstrate any affinity in vitro between peripheral nerve substance and virus have yielded negative results;[54] but this is also true of central nervous system tissue, such as cord, which fails to fix virus in vitro.[55] While there is as yet no basis for a direct chemical interaction between poliomyelitis virus and nerve tissue, an unquestionable and selective attraction of the virus by intact peripheral nerve endings has been shown in so many experiments that it may be accepted as an established fact.[56] To this can be added, as a next consideration, the fact that peripheral nerves possess the ability to conduct virus centripetally to the anterior horn. Whether such migration of virus is entirely passive or involves active multiplication, en route, remains still uncertain. However, nothing in the experimental evidence is inconsistent with an assumption that the virus may, at times, not penetrate beyond the myoneural junction and produce a state of reversible or reparable lack of contractility which, after all, is so highly characteristic of the paralytic pattern in human poliomyelitis.

Lesions in the skeletal muscle of animals infected with murine poliomyelitis virus were first demonstrated by Rustigian and Pappenheimer,[57] who injected Col. SK virus intramuscularly into mice. Within a few hours, even before the appearance of paralytic symptoms, the local injection of virus was followed by the development of an extensive myositis involving most of the muscle groups in the injected area. The pathologic process consisted of a widespread necrosis of individual muscle fibers, accompanied by a marked inflammatory cellular response. Its occurrence could be effectively prevented by homologous immune serum, indicating the specific nature of the lesion. A similar myositis could be produced with a high-titered strain of Theiler's virus (GDVII), but no corresponding lesions were obtained with the Lansing strain or with a low-titered Theiler strain (OT). A number of neurotropic viruses, other than poliomyelitis virus, gave either no local reaction in the muscle or a different cytological response. We have been able to confirm these results in guinea pigs following intramuscular injection of Col. SK virus (Fig. 2), except that development of the lesion requires more time, in keeping with the lower virulence of the virus and the slower course of the experimental disease in guinea pigs as compared with mice.[58] It was also found that the lesion was strictly local in the sense that it occurred only in the initially paralyzed leg and not in subsequently paralyzed extremities. Nor could it be obtained when paralysis was produced

by intraperitoneal injection of the virus. It would seem from these data that the ability to produce myositis is characteristic of and limited to highly virulent strains of the poliomyelitis virus family, i.e., agents, which also present other evidence of possessing well-developed viscerotropic properties.

Fig. 2.

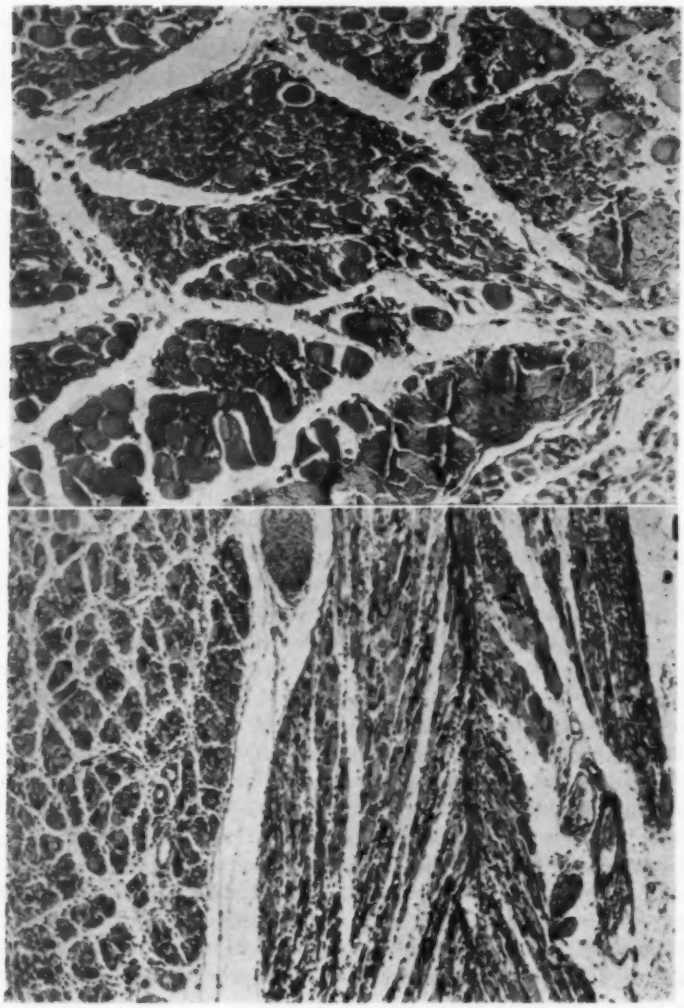

Fig. 3.

Fig. 2.—Myositis produced in a guinea pig (No. 1318) by intramuscular injection of Columbia SK brain passage virus (paralyzed arm, seven days after injection).

Fig. 3.—Myositis and muscle degeneration produced by intraperitoneal injection of Coxsackie virus (TT strain) in a suckling mouse (paralyzed leg, six days after injection).

New interest was added to these observations with the advent of the Coxsackie group of viruses.[38, 39] The various strains within this group (at present brought together under this term for want of a better designation) all have the outstanding property of paralyzing suckling mice, guinea pigs, or hamsters with the production of a massive myositis in the affected limbs, with or without concomitant lesions in the central nervous system (Fig. 3). While the pathologic changes in the skeletal muscles are quite similar to those previously described for infection with Col. SK virus, the Coxsackie type strains appear to be even more myotropic, since muscular lesions may regularly be obtained through infection by routes other than direct introduction of the virus into the muscle. This difference, however, is more apparent than real. For, when Col. SK or EMC virus is harvested from infected spleen and carried as a spleen strain peripherally over several mouse passages, a highly viscerotropic variant is obtained which also induces typical myositis in the paralyzed limbs following intraperitoneal injection of the virus.[58] In other words, it would seem as if the proportion between neurotropic and viscerotropic qualities of a given viral strain may not be fixed but variable, subject to the modifying influence of tissue environment.

Discovery of the Coxsackie group of viruses is still too recent for critical evaluation. However, Dalldorf's original findings have not only been confirmed, but virus of this type has been widely isolated from the stools of paralytic and nonparalytic patients routinely diagnosed as cases of poliomyelitis. Isolations from individual fecal samples have usually yielded either the new mouse virus or the classical monkey virus, but cases are now on record, in increasing numbers, in which both viruses are encountered side by side in the same specimen. Comparative neutralization tests with patients' sera have not been performed on a large scale to indicate how frequently antibodies against both viruses occur together in the same individual. The present trend of opinion is to interpret these observations as mixed infections with classical virus and a new agent, capable of producing human infection with epidemiological and clinical features that are indistinguishable from what has heretofore been called poliomyelitis. Further progress in this field will be watched with intense interest for it is evident that the Coxsackie group of viruses occupies a key position in the problem of neurotropic and viscerotropic variation of poliomyelitis virus.

4. Myocardial involvement: Pathologic study of the heart muscle in experimental poliomyelitis has received scant or no attention. Except for Sanz Ibanez's[45] description of interstitial myocarditis in guinea pigs infected with Col. SK virus, references to heart lesions are few and, as a rule, are merely part of a general consideration of the visceral pathology in the experimental disease. Myocardial lesions have not been observed with low-titered neurotropic strains, but Y-SK virus has once been isolated from the heart of an experimentally infected infant rhesus monkey.[59] More definite information, however, has come from a study of a presumable variant of Y-SK virus obtained through passage in infant mice. This agent produces typical flaccid paralysis in intracerebrally infected rhesus monkeys with extensive myocardial involvement[60] (Figs. 4 and 5). Few freshly isolated human strains have as yet been examined for their

ability to produce myocarditis in experimental infection. However, two strains of poliomyelitis virus, recently isolated from cord or heart in fatal cases,[27] and a third strain, isolated from the paralyzed muscle during the acute stage of

Fig. 4.

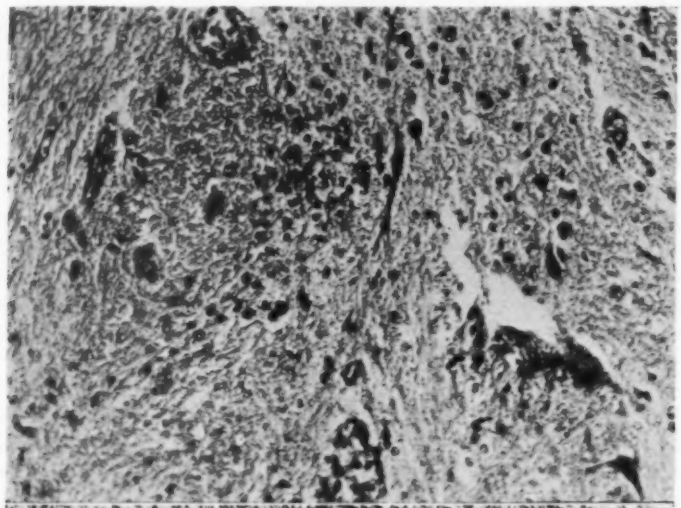

Fig. 5.

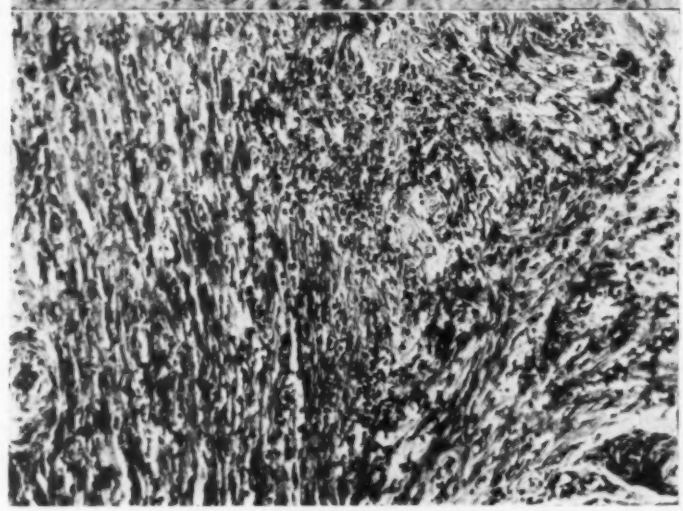

Fig. 4.—Rhesus AR100. The monkey has almost complete paralysis of the left arm and leg, six days after intracerebral injection with Y-SK mouse virus (V suckling mouse passage). This is a section through the lumbar cord showing neuronophagia of ganglion cells and perivascular infiltration in anterior horn.

Fig. 5.—Rhesus AR79. The monkey died with generalized weakness, following intracerebral injection with Y-SK mouse virus (I suckling mouse passage). This is a section through the heart showing focal myocarditis with interstitial cellular infiltration and necrosis of muscle fibers.

the disease,[18] have produced paralysis and myocardial involvement in some of the cynomolgus subpassages. In the several instances of experimental poliomyelitic myocarditis which have been mentioned, the pathologic changes are closely similar to the type of lesion described in the human disease. While the above data suggest a definite association of myocarditis with central nervous system lesions in the pathologic responses induced by certain strains of poliomyelitis virus, further work is urgently needed to elucidate the mechanism of this relationship.

The classical example of myocardial involvement in infection with poliomyelitis or poliomyelitis-like virus is, of course, EMC virus.[34] In the original host, the myocarditis-producing property of this particular virus apparently overshadowed its ability to produce paralysis which became only manifest upon subsequent transfer to laboratory animals. In its early rodent passages the virus combined marked neurotropism and viscerotropism, inducing both myocarditis and encephalomyelitis in mice, hamsters, and guinea pigs. Rapid serial passages by the intracerebral route soon led to fixation so that, beginning with the fifty-second generation, the strain produced only paralysis but no longer myocarditis. However, when the virus was harvested from infected spleen and carried as a spleen-strain peripherally in mice, nervous and myocardial lesions appeared once more in the paralyzed animals.[58] These experiments suggest: (1) that EMC virus is an agent of complex structure, possessing both neurotropic and viscerotropic qualities; (2) that the viscerotropic quality may be dormant during intracerebral passages; and (3) that the lost viscerotropic quality may be restored through propagation on extraneural tissue. Identical results are obtained when Col. SK virus is subjected to the same experimental procedures. What adds to the significance of these observations is the fact that the spleen (visceral) strains of EMC and Col. SK viruses produce not only myocarditis but also extensive myositis in the paralyzed skeletal muscle following intraperitoneal injection of mice. The described phenomena illustrate the inherent variability of the viruses in this group. Besides, they offer evidence for believing that strains may be so manipulated as to close the gap with the Coxsackie group of viruses which exhibit a similar, unusual degree of myotropism.

Changes in tissue tropism, occurring under corresponding experimental conditions, have been reported for other viruses. Examples are, on the one hand, the gain of neurotropism and loss of viscerotropism for yellow fever virus as the result of intracerebral passage in mice; on the other, the loss of neurotropism and gain of dermotropism for Western equine encephalomyelitis virus when the latter is transmitted serially in the foot pad of guinea pigs. The analogous results obtained with Col. SK and EMC viruses, therefore, suggest that viruses belonging to the poliomyelitis group may possess similar facilities for exchange of tissue affinities (nervous tissue, muscle tissue, lymphatic tissue).

CONCLUSIONS

In presenting the subject matter of this review it has been expedient to separate, for discussion, pertinent information concerning the disease in human

beings from corresponding experimental facts. This division is, of course, purely artificial and the two sets of data should be resynthesized so as to permit a full perspective of the many facets of the problem. When the data are surveyed from this vantage point, clinical experience and laboratory observations will be found, on the whole, in excellent agreement. In some instances the clinical approach has proceeded beyond the present stage of experimental reproducibility; in others, results derived from experimental studies are still waiting for clinical evaluation. Undoubtedly, such gaps in our knowledge will be closed as time goes on, promising eventually perfect coordination. Among the unsettled issues that ought to receive intensified attention in future studies of paralytic and nonparalytic cases are: (1) presence of an early, transient viremia, (2) pathologic reactions in the muscular intestinal wall, (3) chemical dysfunction or structural defects at the myoneural junction, (4) cardiac dysfunction or structural lesions in the heart muscle, and (5) constitutional factors of age and predisposition modifying the peripheral response.

One aspect of the problem which deserves special emphasis is the gradually accumulating evidence that infantile paralysis is probably not a homogenous nosological entity; as a corollary, it seems logical that the virus which causes Heine-Medin disease may also be a heterogenous agent. Obviously, the collective term of "poliomyelitis" includes a number of morbid conditions, ranging from almost imperceptible extraneural involvement, to reversible pathologic changes at the myoneural junction, to irreversible destruction of ganglion cells in the anterior horn. The varying degrees of extensity and intensity of the infectious process seem to stand in direct proportion to corresponding levels of viscerotropism and neurotropism of the virus. While it is still correct that spread of the virus throughout the central nervous system, once this area has been invaded, follows the pattern of a neurotropic and even neuronotropic agent, it is almost certain that the virus which is responsible for the initial systemic phase of the disease can no longer be considered neurotropic in the strict sense of the word. Whether poliomyelitis virus occurs in more than one form, blending into strains with viscerotropic and neurotropic phases, it is too early to say unless actual conversion of one into the other has been demonstrated at will. An alternate hypothesis, decidedly less attractive, would be to postulate the existence of a group of separate diseases with grotesquely superimposed epidemiological traits and similarity in clinical symptoms, but of different etiology. Whatever the final answer may be, it seems a reasonable statement at this time that the highly specialized, neurotropically fixed virus, which has been maintained in the past by intracerebral passage in rhesus monkeys, is more likely a laboratory artifact than the agent which causes the natural disease in man.

Considering the disease process as one which begins with peripheral manifestations and terminates with central nervous system involvement, but halts characteristically at various midway points, the available evidence may be pieced together to suggest the following sequence of events: The first stage of infection is probably represented by entrance of the virus through the alimentary tract, its penetration through the intestinal mucosa and initial growth within the wall of the gut. At this level, infection remains asymptomatic, being main-

tained at a silent portal of entry. The second stage, ushered in as the result of a breakdown of local mechanisms of defense in the lymphatic system, might lead to transient viremia with rapid removal of the virus from the bloodstream by means of filtration and fixation in muscle tissues. Coincident with virus multiplication in skeletal and heart muscle, a number of diverse peripheral lesions may set in, thus advancing the process to the symptomatic stage of reparable dysfunction. The third, or final, stage of the infection would be attained only under exceptional conditions which permit excessive growth of the virus, subsequent passage across the myoneural synapsis, and eventual transport along peripheral nerves to the spinal cord with irreparable destruction of the ganglion cells in the anterior horn. The implied mechanism is no more circuitous than that suggested by Hurst[63] for another viscerotropic-neurotropic virus, i.e., equine encephalomyelitis. It is conceivable that different strains of poliomyelitis virus, in consonance with the degree of their inherent neurotropic and viscerotropic qualities, may alter the cycle of progression, imitating either the indiscriminate spread across blood vessels, which is characteristic of many encephalitides, or approaching the picture of strict neuronal dissemination, which prevails in rabies. In any event, the pattern is sufficiently flexible to visualize a possibility that neurogenic and myogenic defects may conjointly determine the paralytic involvement of synergistic and antagonistic groups of muscle.

The suggested mechanism for the pathogenesis of poliomyelitis is based upon a concept which stands in stark opposition to earlier beliefs (Faber[64]) according to which the disease should be regarded as an essential and primary affection of the central nervous system. However, the weight of the evidence presented in this review makes such a viewpoint less and less tenable and tips the scales heavily in favor of adopting a cautious and critical attitude. Our understanding of poliomyelitis, in the past, has been hampered too much by a lack of precise information. Actually, the history of this disease has been marked by periods of violent disagreement among scientific workers and by sharp dissension within the ranks of the medical profession. The subject is of keen interest to clinicians and laboratory workers alike and progress will be measured by the extent of cooperation between the two. Until the final word has been said, it is to be hoped that, in the future, students of poliomyelitis will preserve an open mind and maintain an open door in their efforts to unravel the mysteries of this baffling disease.

REFERENCES

1. Peabody, F. W., Draper, G., and Dochez, A. R.: A Clinical Study of Acute Poliomyelitis, Monogr. Rockefeller Institute for Med. Res., No. 4, 1912.
2. Burrows, M. T.: Is Poliomyelitis a Disease of the Lymphatic System? Arch. Int. Med. **48**: 33, 1931.
3. Landon, J. F., and Smith, L. W.: Poliomyelitis, New York, 1934, The Macmillan Company.
4. Paul, J. R., Salinger, R., and Trask, J. D.: Abortive Poliomyelitis, J. A. M. A. **98**: 2262, 1932.
5. Wenner, H. A., and Casey, A. E.: Community Study of Carriers in Epidemic Poliomyelitis, J. Clin. Investigation **22**: 117, 1943.
6. Kling, C., Levaditi, L., and Lépine, P.: La pénétration de virus poliomyélitique à travers la muqueuse du tube digestif chez le singe et sa conservation dans l'eau, Bull. Acad. de méd., Paris **102**: 158, 1929.

7. Sabin, A. B., and Ward, R.: Poliomyelitis in a Laboratory Worker Exposed to the Virus, Science **94**: 113, 1941.
8. Melnick, J. L., and Horstman, D.: Active Immunity to Poliomyelitis in Chimpanzees Following Subclinical Infection, J. Exper. Med. **85**: 287, 1947.
9. Casey, A. E., Fishbein, W. I., Gordon, F. B., and Schabel, F. M.: Clinical Manifestations of Infection With Poliomyelitis Virus, J. A. M. A. **138**: 865, 1948.
10. Pohl, J. F.: The Peripheral Disease of Poliomyelitis, J. Bone & Joint Surg. **29**: 1027, 1947.
11. Carey, E. J., Massopust, L. C., Zeit, W., and Haushalter, E.: Anatomic Changes of Motor Nerve Endings in Human Muscles in Early Poliomyelitis, J. Neuropath. & Exper. Neurol. **3**: 121, 1944.
12. Sanz Ibanez, J.: Estudio de la sinapsis minoneural y componentes nerviosos en músculos humanos paraliticos por paralisis infantil, Trab. Inst. Cajal de inv. biol. **37**: 259, 1945.
13. Dublin, W. B., Bede, B. A., and Brown, B. A.: Pathologic Findings in Nerve and Muscle in Poliomyelitis, Am. J. Clin Path. **14**: 266, 1944.
14. Kopits, I.: Beiträge zur Muskelpathologie, Arch. f. Orthoph. **27**: 277, 1929.
15. Hassin, G. B.: Landry's Paralysis: Its Clinical and Pathological Features, J. Neuropath. & Exper. Neurol. **2**: 293, 1943.
16. Quoted by: Gifford, R., and Dalldorf, G.: Creatinine, Potassium, and Virus Content of the Muscles Following Infection With the "Coxsackie virus," Proc. Soc. Exper. Biol. & Med. **71**: 589, 1949.
17. Clawson: Quoted by Bell, E. T.: The Progressive Pathology of Poliomyelitis, Proc. First Internat. Poliomyelitis Conference, New York, 1948.
18. Jungeblut, C. W., and Stevens, M. A.: Attempts to Isolate Poliomyelitis Virus from the Paralyzed Muscle of Patients During the Acute Stage of the Disease, Am. J. Clin. Path. (In press.)
19. Buchthal, F.: Some Aspects of the Pathological Physiology of Poliomyelitis, Proc. First Internat. Poliomyelitis Conference, New York, 1948.
20. a) Saphir, O., and Wile, S. A.: Myocarditis in Poliomyelitis, Am. J. M. Sc. **203**: 781, 1942.
    b) Saphir, O.: Visceral Lesions in Poliomyelitis, Am. J. Path. **21**: 99, 1945.
21. Peale, A. R., and Lucchesi, P. F.: Cardiac Muscle in Poliomyelitis, Am. J. Dis. Child. **65**: 733, 1943.
22. Dolgopol, V. B., and Cragan, M. D.: Myocardial Changes in Poliomyelitis, Arch. Path. **46**: 202, 1948.
23. Ludden, T. E., and Edwards, J. E.: Carditis in Poliomyelitis; An Anatomic Study of Thirty-five Cases and Review of the Literature, Am. J. Path. **25**: 357, 1949.
24. Boncek, R. J., Bailey, A. A., Burchell, H. B., and Edwards, J. E.: Myocardial Disease in Acute Poliomyelitis, Proc. Staff Meet., Mayo Clin. **24**: 495, 1949.
25. a) Battro, A., Cibils Aguirre, R., and Mendy, J. C.: Estudio electrocardiográfico en la enfermedad de Heine-Medin, An. de Inst. Invest. fis. apl. a la pat. humana **5**: 7, 1943.
    b) Firpi, M. A., Murphy, F. J., Walsh, V. J., and Anderson, W. S.: Survey of Poliomyelitis Cases for 1948, Clin. Proc. Child. Hosp. (Washington, D. C.) **5**: 239, 1949.
26. Gefter, W. I., Leaman, W. G., Jr., Lucchesi, P. F., Maher, I. E., and Davorin, M.: The Heart in Acute Anterior Poliomyelitis, Am. Heart J. **33**: 228, 1947.
27. Jungeblut, C. W., and Edwards, J. E.: In preparation.
28. Ward, R., Horstman, D., and Melnick, J. L.: The Isolation of Poliomyelitis Virus from Extraneural Sources: IV. Search for Virus in the Blood of Patients, J. Clin. Investigation **25**: 284, 1946.
29. a) Armstrong, C.: The Experimental Transmission of Poliomyelitis to the Eastern Cotton Rat, Sigmodon hispidus hispidus, Pub. Health Rep. **54**: 1719, 1939.
    b) Armstrong, C.: Successful Transfer of the Lansing Strain of Poliomyelitis Virus from the Cotton Rat to the White Mouse, Pub. Health Rep. **54**: 2302, 1939.
30. Jungeblut, C. W., and Dalldorf, G.: Experimental and Epidemiological Observations on the Possible Significance of Rodents in a Suburban Epidemic of Poliomyelitis, Am. J. Pub. Health **33**: 169, 1943.
31. Jungeblut, C. W., and Sanders, M.: Studies of a Murine Strain of Poliomyelitis Virus in Cotton Rats and White Mice, J. Exper. Med. **72**: 407, 1940.
32. a) Toomey, J. A., and Takacs, W. S.: Experiments With the SK Strain of Poliomyelitis in Smaller Animals, J. Bact. **43**: 87, 1942.
    b) Toomey, J. A.: Personal communication.
33. Melnick, J. L., and Ward, R.: Adaptation of Poliomyelitis Strains to Rodents With a Word on Nomenclature, Federation Proc. **7**: 308, 1948.
34. Schmidt, E. C. H.: Virus Myocarditis; Pathologic and Experimental Studies, Am. J. Path. **24**: 97, 1948.

35. a) Dick, G. W. A., Smithburn, K. C., and Haddow, A. J.: Mengo Encephalomyelitis Virus: Isolation and Immunological Properties, Brit. J. Exper. Path. **29**: 547, 1948.
b) Dick, G. W. A.: Mengo Encephalomyelitis Virus: Pathogenicity for Animals and Physical Properties, Brit. J. Exper. Path. **29**: 559, 1948.
c) Dick, G. W. A., Best, A. M., Haddow, A. J., and Smithburn, K. C.: Mengo Encephalomyelitis; A Hitherto Unknown Virus Affecting Man, Lancet **255**: 286, 1948.
36. Dick, G. W. A.: The Relationship of Mengo Encephalomyelitis, Encephalomyocarditis, Columbia SK and MM Viruses, J. Immunol. **62**: 375, 1949.
37. Warren, J., Smadel, J. E., and Russ, S. B.: The Family Relationship of Encephalomyocarditis, Columbia SK, MM, and Mengo Encephalomyelitis Viruses, J. Immunol. **62**: 387, 1949.
38. a) Dalldorf, G., and Sickles, G. M.: An Unidentified Filtrable Agent Isolated from the Feces of Children with Paralysis, Science **108**: 61, 1948.
b) Dalldorf, G., Sickles, G. M., Plager, H., and Gifford, R.: A Virus Recovered from the Feces of "Poliomyelitis" Patients Pathogenic for Suckling Mice, J. Exper. Med. **89**: 567, 1949.
39. Melnick, J. L., Shaw, E. W., and Curnen, E. C.: A Virus Isolated from Patients Diagnosed as Nonparalytic Poliomyelitis or Aseptic Meningitis, Proc. Soc. Exper. Biol. & Med. **71**: 344, 1949.
40. Jungeblut, C. W.: Problems of Classification of Poliomyelitis Virus. (In preparation).
41. Sanders, M., and Jungeblut, C. W.: Studies in Rodent Poliomyelitis; II. Cultivation of the Murine Strain of SK Poliomyelitis Virus, J. Exper. Med. **75**: 631, 1942.
42. a) Schultz, E. W., and Enright, J. B.: Cultivation of the Murine SK Strain of Poliomyelitis Virus in Developing Eggs, Proc. Soc. Exper. Biol. & Med. **63**: 8, 1946.
b) Enright, J. B., and Schultz, E. W.: Further Observations on the Cultivation of Strains of Poliomyelitis Virus in Developing Eggs, Proc. Soc. Exper. Biol. & Med. **66**: 541, 1947.
43. Enders, J. F., Weller, T. H., and Robbins, F. C.: Cultivation of the Lansing Strain of Poliomyelitis Virus in Cultures of Various Human Embryonic Tissues, Science **109**: 85, 1949.
44. Weller, T. H., Robbins, F. C., and Enders, J. F.: Cultivation of Poliomyelitis Virus in Cultures of Human Foreskin and Embryonic Tissues, Proc. Soc. Exper. Biol. & Med. **72**: 153, 1949.
45. Sanz Ibanez, J.: Poliomyelitis Experimental, Trab. del Inst. Cajal de invest. biol. **36**: 137, 1944.
46. Jungeblut, C. W.: Mechanism of Infection in Rodent Poliomyelitis in Relation to Age and Portal of Entry, J. Infect. Dis. **81**: 282, 1947.
47. Evans, C. A., and Chambers, V. C.: Growth of Neurotropic Viruses in Extraneural Tissues; I. MM Virus in the Feet of Hamsters, Proc. Soc. Exper. Biol & Med. **68**: 436, 1948.
48. Gifford, R., and Dalldorf, G.: Creatinine, Potassium, and Virus Content of the Muscles Following Infection With "Coxsackie Virus," Proc. Soc. Exper. Biol. & Med. **71**: 589, 1949.
49. Casals, J., Olitsky, P. K., and Murphy, L. C.: Hemagglutination and Complement Fixation With Type I and II Albany Strains of Coxsackie Virus, Proc. Soc. Exper. Biol. & Med. **72**: 636, 1949.
50. O'Leary, J. L., Heinbecker, P., and Bishop, G. H.: Nerve Degeneration in Poliomyelitis; Physiologic and Histologic Studies on the Roots and Nerves Supplying Paralyzed Extremities of Monkeys During Acute Poliomyelitis, Arch. Neurol. & Psychiat. **28**: 272, 1932.
51. Chor, H.: Nerve Degeneration in Poliomyelitis; Changes in Motor Nerve Endings, Arch. Neurol. & Psychiat. **29**: 344, 1933.
52. Toomey, J. A., and Weaver, H. M.: Poliomyelitis Virus and Degeneration of Peripheral Nerves, Am. J. Dis. Child. **53**: 79, 1937.
53. a) Carey, E. J.: Morphologic Effects of Poliomyelitis Virus Upon Motor End Plates in the Monkey, Proc. Soc. Exper. Biol. & Med. **53**: 3, 1943.
b) Carey, E. J.: Studies on Ameboid Motion and Secretion of Motor End Plates; IV. Anatomic Effects of Poliomyelitis on the Neuro-muscular Mechanism in the Monkey, Am. J. Path. **20**: 961, 1944.
54. Toomey, J. A., Tischer, L. A., and Takacs, W. S.: Attempts to Produce Absorption of Poliomyelitis Virus by Peripheral Nerves in Vitro, Am. J. Dis. Child. **64**: 1008, 1942.
55. Jungeblut, C. W.: The Effect of Concentration and of Various Tissue Constituents on the Virulence of the Poliomyelitis Virus, J. Immunol. **22**: 99, 1932.
56. De Robertis, E., and Schmitt, F. O.: An Electronmicroscope Study of Nerves Infected With Human Poliomyelitis Virus, J. Exper. Med. **90**: 283, 1949.

57. Rustigian, R., and Pappenheimer, A. M.: Myositis in Mice Following Intramuscular Injection of Viruses of the Mouse Encephalomyelitis Group and of Certain Other Neurotropic Viruses, J. Exper. Med. **89**: 69, 1949.
58. Jungeblut, C. W., and Steenberg, E.: Neurotropic and Viscerotropic Strains of Columbia SK and Encephalomyocarditis Virus, Arch. Path. **49**: 574, 1950.
59. Horstman, D. M., Melnick, J. L., Ward, R., and Sá Fleitas, M. J.: The Susceptibility of Infant Rhesus to Poliomyelitis Virus Administered by Mouth; A Study of Distribution of Virus in Tissues of Orally Infected Animals, J. Exper. Med. **86**: 309, 1947.
60. Jungeblut, C. W.: Unpublished data.
61. Jungeblut, C. W., Karowe, H. E., and Braham, S. B.: Further Observations on Blood Grouping in Poliomyelitis, Arch. Int. Med. **26**: 67, 1947.
62. Gsell, O.: Abortive Poliomyelitis; Rein abortive und nicht-paretische Formen der Heine-Medin'schen Krankheit, Leipzig, 1938, Georg Thieme.
63. Hurst, E. W.: Infection of the Rhesus Monkey (M. mulatta) and the Guinea Pig With the Virus of Equine Encephalomyelitis, J. Path. and Bact. **42**: 271, 1936.
64. Faber, H. K.: Discussion of Poliomyelitis; Pathogenesis of the Early Stage, Proc. First Internat. Poliomyelitis Conference, New York, 1948.

Psychologic Aspects of Pediatrics

DIAGNOSTIC VALUE OF THREE DRAWING TESTS FOR CHILDREN

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INFORMATION concerning the emotional, personality, and developmental status of children may be obtained from the use of pencil and paper drawing tests. These tests are easily given and readily interpreted. Certain of the tests have been standardized so that in most instances a rapid and accurate estimation of mental age may be made. In addition, the drawings of children tend to mirror their own problems, whether they be of physical or emotional nature.

The tests are of two general types, the first in which the child is asked to draw a specific object such as a square or a man; the second in which he is asked to draw anything he wishes. This division is arbitrary, and actually some specific stimuli (i.e. "draw a fear") demanding a drawing in abstraction take on the qualities of both.[1] Abstractions and spontaneous drawings of both children and adults offer fascinating study in symbolism and practical value in therapy.[2-5] The specific stimuli tests, however, lend themselves more readily to standardization and ease of administration.

GESELL DRAWING TESTS

Specific drawings are utilized in the Gesell scale as an index of maturation.

At Age	*The Child Can*
18 months	Scribble spontaneously
2 years	Imitate the vertical and circular stroke
3 years	Copy the circle
4 years	Copy the cross
5 years	Copy the square
6 years	Copy the triangle
7 years	Copy the diamond

This is essentially the progression seen in other tests, the Kuhlmann-Binet, the Merrill-Palmer, and the Stanford-Binet. In this way an approximate estimate of the visual-motor maturational level may be quickly obtained. If a 5-year-old child can do no more than copy a circle, we know that he is approximately two years retarded in his visual-motor maturation.

Two additional specific stimuli tests of great value are the Bender visual-motor Gestalt test, and the Goodenough "draw a man" test. These are used routinely on the Children's Service of Bellevue Psychiatric Hospital and will

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be discussed here. Full discussion of drawings of children will appear in a forthcoming book by Dr. Lauretta Bender on *Techniques in Child Psychiatry.*

THE BENDER-GESTALT TEST

This consists of nine geometric figures (Plate I), which are presented one at a time, each on a separate card, and which the patient is asked to copy.[7]

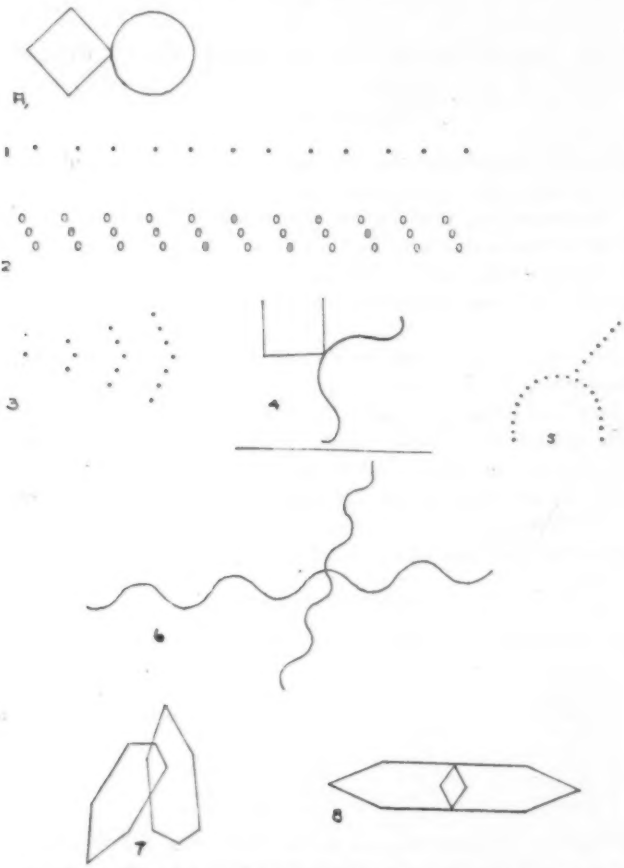

Plate I.—Test figures, Bender visual-motor Gestalt Test. (Reproduced by permission of American Orthopsychiatric Association and Dr. Lauretta Bender.)

No time limit is set. The figures were adapted from the classic studies of the Gestalt psychologist, Max Wertheimer.[8] Simple as it is to give, the test measures a complex series of functions: (a) the visual function, that is the reception of visual stimuli, (b) the integrative function, in which the visual stimuli are sifted through the experiences and the organic matrix of the individual, and thus interpreted, and (c) the motor function, in which the visual percept is

translated into the motor activity of drawing. The resulting configuration "may thus be expected to vary in different maturation or growth levels or in pathological states,"[7] organically or psychologically determined.

Developmentally, there is a progression in the performance of these geometric patterns from a controlled scribble at the age of 3 years, to all the figures clearly and well drawn at age 11 years. The test has been standardized and can be used as a measure of the visual-motor ability between the ages of 4 and 11 years. The following standardization is taken from Lauretta Bender, *A Visual Motor Gestalt Test and Its Clinical Use,* which should be consulted for detailed discussion. The 4-year-old child uses circles or closed loops in horizontal, concentric, mass, or perseverative (repetitive) relationships. At the age of 5 years, circles and loops in perseverative pattern persist, but closed squarelike forms, open circles, and arcs appear. At 6 years, wavy lines can be crossed (Plate I, Fig. 6), and Fig. A, 1, 4, and 5 emerge clearly. By the age of 7 years, all figures are satisfactorily performed except the oblique vertical sequences of Plate I, Fig. 2 (which are completed at ages 9 and 10), the obliquity of Fig. 6 (completed at 8 years), and the obtuse angulation of Fig. 3 (completed at 11 years).

Primitive responses, then, include the appearance of scribbles, the use of loops for dots, lines for dots, loops in massed relationship, perseveration, verticalization of horizontally placed figures and oblique lines, difficulty with angulation in Figs. A, 7, and 8, and difficulty in joining the parts of a figure. The appearance of primitive responses may be due to normal maturational factors; to delay or interference with maturation as in the developmental lags or in the organic states, be they degenerative, traumatic, infectious, or toxic; or to regressions psychologically or organically determined.

BENDER-GESTALT IN ORGANIC STATES

In the organic states, the Bender-Gestalt test is very useful. Developmental lags in the motor area reveal themselves in patterns below the mental age of the child; lags in language function, as in the reading disability, usually show verticalizations and difficulty with angulation; diffuse encephalopathy of acute nature shows uneven regressions which clear up; chronic encephalopathy may show the impulsive quality of the brain-damaged child, or the rigidity and self-criticism with which the child attempts to cover his defect.

Lennie, for example, was 10 years, 6 months old when he did the test in Plate II. He was brought into the clinic at 9 years of age by a tense but determined mother because of a facial tic of at least 3 years duration. He did poorly at school, had no friends, and fought with a younger brother, aged 7. The home situation was a bad one. The father was an inadequate person preoccupied with his own somatic complaints, the mother, a demanding person bewildered and resentful about Lennie's behavior and school failures. The patient was a physically well-developed boy with an I. Q. of 106, who showed marked anxiety and a syndrome which we have come to associate with reading disability, i.e., primitive postural reflexes, mixed dominance, faulty right-left discrimination, difficulty in figure-background tests, and a Bender-Gestalt

drawing which shows clearly difficulty with angulation in Figs. A, 7, and 8, rotational tendencies in Fig. 2, and mass relationship of dots in Fig. 3. This represents a more primitive Gestalt pattern related to a developmental lag in the language function. It shows also the angulation and rotational problems which seem to go with reading disability.

Frances, who was 10½ years old when she drew the Gestalt in Plate III, represents a regression on the basis of an acute toxic reaction. She was an apparently well child until she received homatropine eye drops for refraction over a period of one and one-half days. That night she awoke in terror saying that a man was going to kill her with a knife. The following day she was delirious, in constant agitation, wringing her hands, "plucking things off the wall and off herself." When seen the following day she had a total amnesia for the events of the preceding day; she was oriented to place and person but not to time. She was still terrified about being killed by a man with a knife and was in terror lest the elevated train fall off the tracks. The pupils were widely dilated and fixed to light, pulse was rapid and regular. There was a moderate flushing of the face. Her intelligence was about average. Rorschach examination revealed a picture not unlike that seen in schizophrenia. The Bender-Gestalt test done on the second day of her illness (Plate III) revealed the following regressive features: use of loops for dots (Figs. 1, 2, 3, 5), perseveration (Figs. 1, 2), verticalization (Figs. 2, 6), poor patterning (Figs. 7, 8).

In addition to the survey of each Gestalt figure, the impression of the total Gestalt pattern, the "feel" of the completed group picture, is significant. Plasticity, for example, is an attribute of the primitive Gestalt. The paper seems to catch for a fleeting moment the whirling quality of the primitive perceptual world. This is seen in Frances' Gestalt drawing. Constrictions, inhibitions, and motor impulses also break through into her Gestalt pattern. Defense mechanisms in terms of rigidity and self-criticisms are apparent.

The break through of impulses is evident in Stephen's Bender-Gestalt pattern. Stephen was 10 years old. He had always been a problem; restless, hyperactive, demanding. His mother had had severe toxemia with convulsions during her pregnancy with Stephen and he, immediately following his birth, had had prolonged respiratory difficulty, and is said to have been "blue" for three or four days and required blood transfusions. There was moderate retardation in his motor development. School accentuated his difficulty and his hyperkinesia increased. On examination Stephen was appealing with his wild red hair and freckles. His speech was rapid, movements darting. He investigated all objects in the room, quickly picking them up, "What's this for?" quickly dropping them again. He felt that he was stupid, that "something is wrong with my head," wanted to be helped. His functioning was at a dull normal level with short attention span, poor memory, and poor muscle coordination. Physical examination revealed no focal neurological findings. Electroencephalogram was diffusely abnormal. His Gestalt drawing (Plate IV) shows many primitive features, verticalization, and angulation difficulty, but outstanding is the impulsive, uncontrolled, unpatterned quality of the total

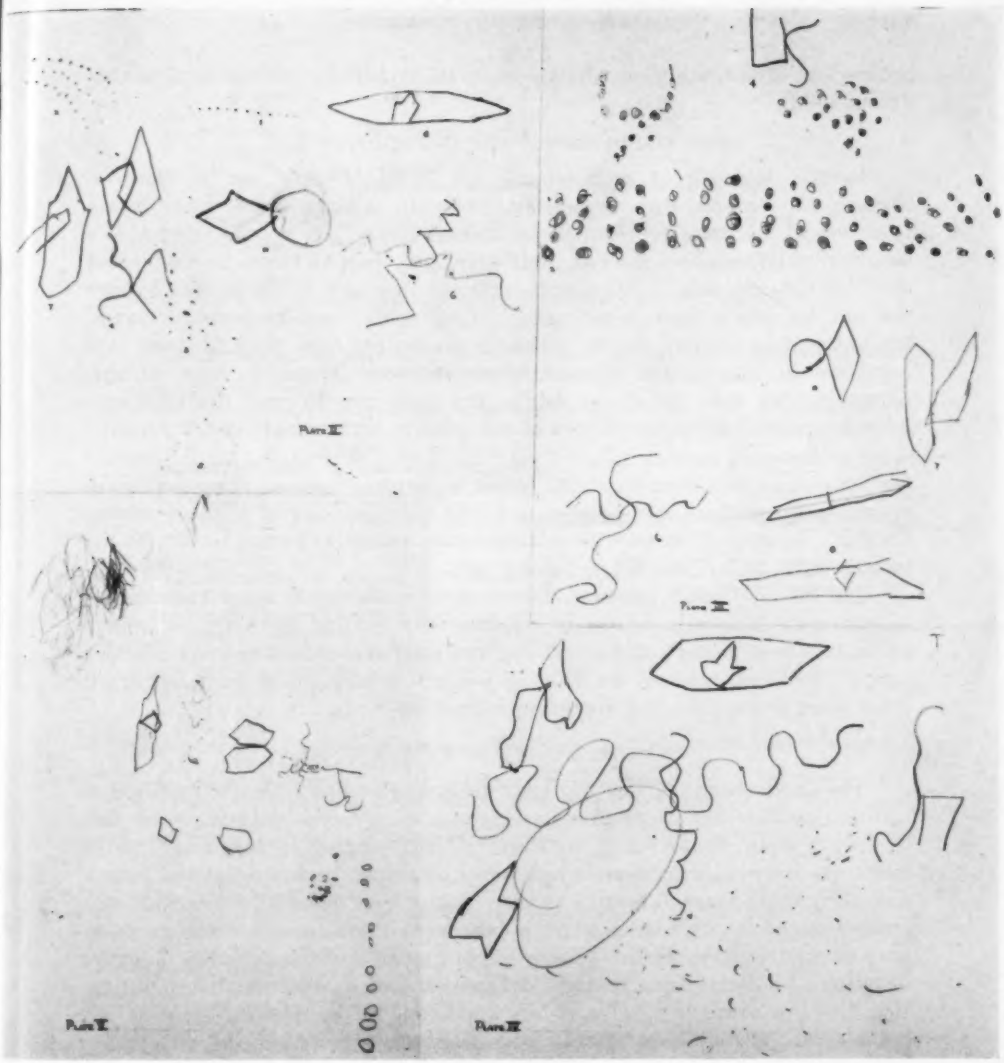

Plate II.—Bender-Gestalt test of a boy 10 years old with a specific reading disability and behavior problem (mental age, Stanford-Binet test, 10 years, 9 months). This drawing shows difficulty in producing correct angulation in the diamond figures (A, 7, 8), rotation of the figure in 2 and 4, uncertainty as to direction in Fig. 6, massed relationship of dots in Fig. 3. This is a primitive pattern. The angulation problem and the rotation are typical patterns found in children with reading disability.

Plate III.—Bender-Gestalt test of a girl 10 years, 6 months old (mental age 10-6) with an acute toxic psychosis following use of homatropine eye drops, showing the use of loops for dots (Figs. 1, 2, 3, 5), perseveration (1, 2), verticalization (2, 6), poor pattern (7, 8). This is also a regressive pattern, more so than Plate II. Note the quality of motion in the total pattern. This quality is also seen in schizophrenia. At this age perseveration and the regressive features bespeak organicity. This child's drawing of a person is seen in Plate IX.

Plate IV.—Bender-Gestalt test of a boy 10 years old, mental age 9 years, 6 months, with brain damage due to prolonged anoxia at birth. This drawing shows primitive features of verticalization, angulation difficulty, and perseveration; but outstanding is the impulsive, uncontrolled, unpatterned quality of the total production. This Gestalt immediately raises the question of an organic, impulse-driven child. His Goodenough drawing is seen in Plate VIII.

Plate V.—Bender-Gestalt test of a boy, 8 years old, with schizophrenia (functioning age 3 years, 6 months), showing marked constriction, at times fading away to a faint scrawl. There is performance as high as age 7 years, however (Fig. A). Separation of Fig. A is also seen. This uneven function from a 7-year age level to an 18-month scrawl, together with the severe constriction, suggests a marked withdrawal, such as that seen in schizophrenia.

production. The Gestalt immediately raises the question of an organic, impulse-driven child.

THE BENDER-GESTALT TEST IN SCHIZOPHRENIA

In the diagnosis of schizophrenia the Bender-Gestalt test is valuable. Norman, for example, drew a constricted Gestalt, at times fading away into a faint scrawl, at times represented by massed loops. He was 8 years old, a beautiful child, chubby cheeked, well developed, but his parents complained that "he does not talk." He did at one time, they said, when he was 3 years old, but his words have faded away. They said he understood commands, but initiated no activity, merely following his mother from room to room. On psychometric examination Norman scored between 3 and 4 years of age. Language tests were failed completely, and until now Norman has been considered a mental defective. Study of the Gestalt, however, (Plate V) revealed some performance as high as the 7-year age level. So that the Bender-Gestalt test tells us at once that this child is not a simple defective. His constricted, uneven patterns from a scribble to a 7-year function suggest a severe schizophrenia. In other children with schizophrenia, a plastic, flowing quality to the total pattern, as in Plate III, is usually seen.

The Bender-Gestalt test then, does more than offer an index of visual-motor maturation. It reveals defects in children with reading disability, it reflects motor impulses, perceptual fluctuations, and emotional difficulties. As Schilder says, "The figure becomes the rallying point in a background composed of all other sense perceptions and vegetative influences."[9]

THE GOODENOUGH "DRAW A MAN" TEST

The Goodenough test was originally devised as a measurement of intelligence utilizing nothing but the child's drawing of a man.[10] The child is simply told to draw a man. Standardized on 3,585 children ranging in age from 4 to 10 years, the drawing can be scored in terms of points, beginning at the year 3 and going to 13 years, 6 months of age. Points were devised by means of "a) observation of the differences which appear to be characteristic of the performance of children at successive ages or school grades, b) formulation of objective definitions or descriptions of these differences, and c) their statistical validation."[10] For example, head and legs appearing in the drawing score as one point each. The addition of arms adds another point, trunk present another. The point items are specific, carefully defined, and in scoring, Goodenough's criteria must be adhered to. Each point represents 3 months of mental age starting at 3 years. A brief scoring key* is:

Class A

Preliminary stage, in which the drawing cannot be recognized as the human figure.
1. Aimless, uncontrolled scribbling
2. Lines somewhat controlled, approaching crude geometrical forms

Class B

Drawings which can be recognized as the human figure.
1. Head present

*From F. L. Goodenough: *Measurement of Intelligence by Drawings*, World Book Company.

2. Legs present
3. Arms present
4a. Trunk present
b. Length of trunk greater than breadth
c. Shoulders indicated
5a. Both arms and legs attached to trunk
b. Legs attached to trunk; arms attached to trunk at correct point
6a. Neck present
b. Outline of neck continuous with that of head, of trunk, or of both
7a. Eyes present
b. Nose present
c. Mouth present
d. Both nose and mouth shown in two dimensions; two lips shown
e. Nostrils indicated
8a. Hair shown
b. Hair present on more than the circumference of the head, and nontransparent; method of representation better than a scribble
9a. Clothing present
b. Two articles of clothing nontransparent
c. Entire drawing free from transparencies when both sleeves and trousers are shown
d. Four or more articles of clothing definitely indicated
e. Costume complete, without incongruities
10a. Fingers shown
b. Correct number of fingers shown
c. Fingers shown in two dimensions, length greater than breadth, and the angle subtended by them not greater than 180 degrees
d. Opposition of thumb shown
e. Hand shown, as distinct from fingers or arms
11a. Arm joint shown: either elbow, shoulder, or both
b. Leg joint shown: either knee, hip, or both
12a. Head in proportion
b. Arms in proportion
c. Legs in proportion
d. Feet in proportion
e. Both arms and legs shown in two dimensions
13. Heel shown
14a. Motor coordination; lines reasonably firm, without marked tendency to overlap at points of junction
b. Motor coordination; lines firmly drawn, correct joining
c. Motor coordination; head outline; more than crude circle
d. Motor coordination; trunk outline; same as above
e. Motor coordination; outline of arms and legs; without narrowing at point of junction with body
f. Motor coordination; features; symmetrical, correct position
15a. Ears present
b. Ears present in correct position and proportion
16a. Eye detail: brow or lashes shown
b. Eye detail: pupil shown
c. Eye detail: proportion
d. Eye detail: glance directed to front in profile drawings
17a. Both chin and forehead shown
b. Projection of chin shown
18a. Profile with not more than one error
b. Correct profile

In Plate VI, for example, there are present head, eyes, ears, nose, mouth, hair, and legs, a total score of 7 points. The point scale can be reduced to mental age, realizing that each point equals 3 months and that the test bases at 3 years of age. Seven points, therefore, equals 21 months, which, plus 3 years, equals 4 years, 9 months. This test, taken solely as a measurement of intelligence, is valuable in itself.

As Dr. Goodenough recognized, however, the drawing of the human figure is also an index of concept formation and may be considered a projection of our concept of ourselves; a representation of our body image, "the picture of

our own body which we form in our mind—the way in which the body appears to ourselves."[11] In short, the drawing of a person is a mirror of the patient's feelings of himself, a mirror which can be viewed by the examiner. In it we can see the child's concept of himself. This is a significant contribution, for the body image concept is not only biologically determined in laws of growth and development and is therefore constitutionally limited, but it is constantly modified in the light of perceptual and social experience and, consciously or unconsciously, modifies and gives emotional value to new experience. So that, in the drawing of the human figure, we see reflected perceptual and personality problems, problems in the control of patterned movements (motility). Also reflected are compensatory efforts; efforts at control of impulses with rigidity, fears with withdrawal or aggression.

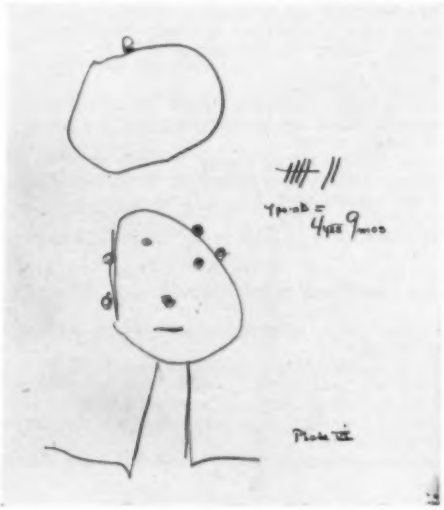

Plate VI.—Goodenough drawing of a normal child, 4 years, 9 months of age.

Attempts have been made to standardize the meaning of the various items in the drawing of the human figure. Werner Wolf, with his background in cryptography has emphasized quality of line.[12] Karen Machover[13] discusses the significance of "patterns of drawing traits" as they appear in body parts, attitudes, and positioning. But, especially with children, no "check list" can be given. If the observer tries to understand what is the body image concept represented in each drawing, what are its outstanding features, he will understand more of his patient's problems.

GOODENOUGH DRAWING IN ORGANIC STATES

In children with organic brain pathology, be it developmental, infectious, degenerative, traumatic, toxic, or anoxic, certain common problems exist. The integration of various stimuli is interfered with, muscle tone may vary, anxiety

is great, efforts at control are used. These reveal themselves in the Goodenough drawing.

Janet, for example, was a bright, 7-year-old girl who came to our ward five months after the onset of a severe measles encephalitis. She was euphoric, chatting continually but unintelligibly. There were frequent bursts of hiccoughs and increased muscle tone in the right lower extremity. Her deep reflexes on the right were greater than those on the left and there was an inconstant right Babinski. Janet's drawings (Plate VII) were also pulled to the right, but as she compensated for her own tonic pull so did the Goodenough figure compensate in its position on the page, until it came to stand upright. In the drawing we can see, however, how rigid and compulsive was the defense she still used to maintain her upright posture. One and one-half years after her illness, the figure was less rigid and was actually balanced on ice skates. We see in this series the predominant tonus problem and the disorganization due to an acute brain disease, and also how the Goodenough drawing became more intact as the disease subsided. Lauretta Bender has shown that in chronic epidemic encephalitis the disorganization in body image may be so great that the Goodenough drawing may be two years below the mental age of the child.

Stephen, the 10-year-old boy whose Bender-Gestalt drawings were discussed above, offers an example of a chronic brain disease, emphasizing, particularly, difficulties in perception. Stephen is impulse-driven but in addition he cannot make meaningful patterns of the mass of stimuli which surround him. He says, "There's something wrong with my head." And we see in his drawing (Plate VIII) a tremendous head dominating the picture. With this alone we could suspect that this child has "trouble with his head." There are other interesting features to Stephen's drawing; the small hands, the figure cut off at the waist, the sun in the corner, all of which reveal further problems of impulse control, aggression, his wish for a father. The outstanding feature, however, is the emphasis on the head.

Motility problems, i.e., the control of patterned movement, are represented in the drawing of Frances, the 10½-year-old girl who, following the installation of homatropine eye drops for refraction, developed an acute toxic reaction resembling schizophrenia. The drawing (Plate IX) gives the impression of motion in a whirling vortical movement. Emphasis is shifted to the periphery and the trunk just manages to hold the peripheral structures from flying apart. Actually, this corresponds to the somatic sensations of the patient.

GOODENOUGH DRAWING IN SCHIZOPHRENIA

Schizophrenia also presents body image problems. Motility problems and peripheral structures are often emphasized, as in Frances' drawing. Extremely regressive drawings or extremely precocious ones are common, bizarre figures, are almost diagnostic, and introjected bodies, like the devil inside the abdomen, may be present. There is occasionally seen a confusion in ego boundary, that is, an inability to separate oneself from the world in space. Mary, for example, was 5 years old. She was brought to the Clinic by a weary grandmother because she would not eat solid foods, was in constant motion, would not keep her

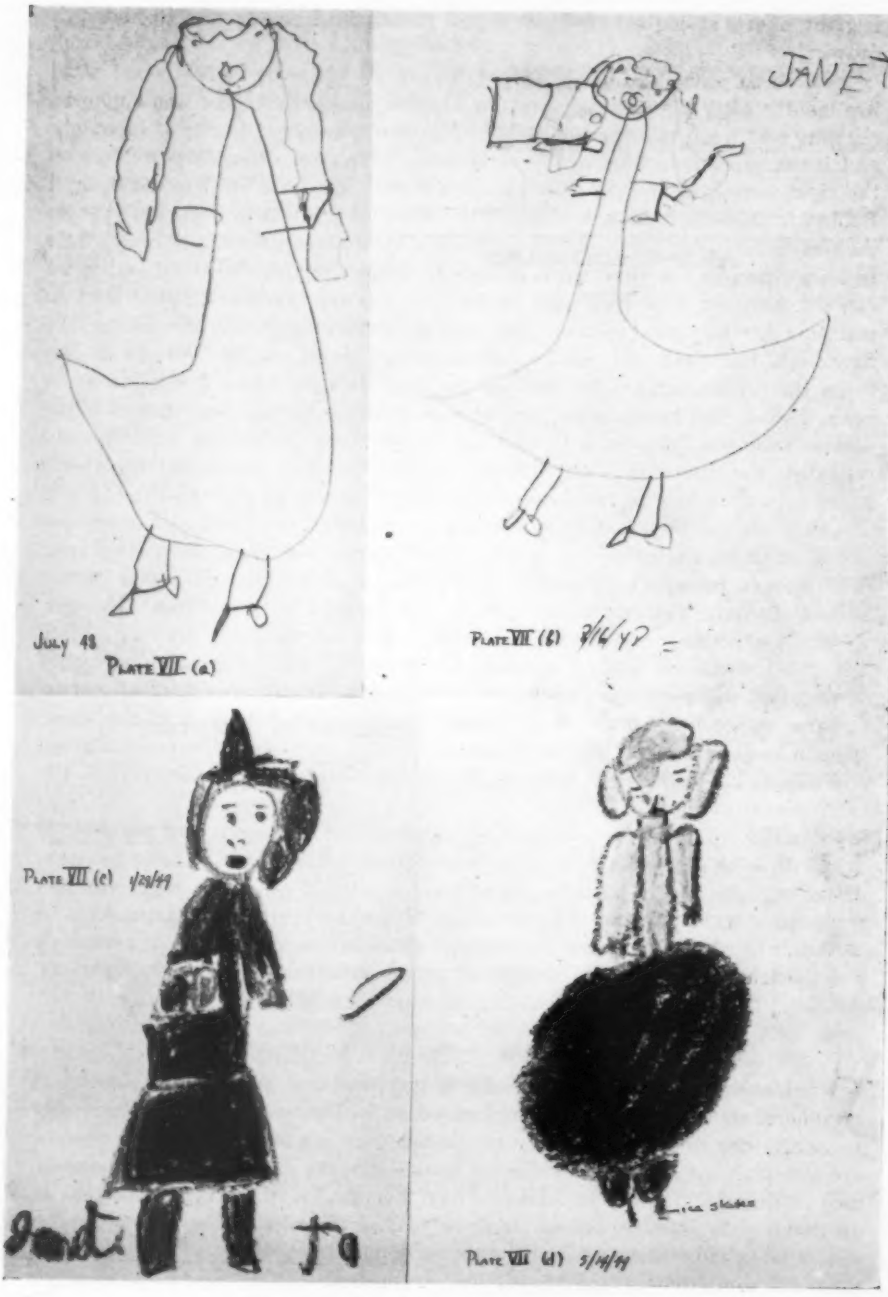

Plate VII.—(*For legend see opposite page.*)

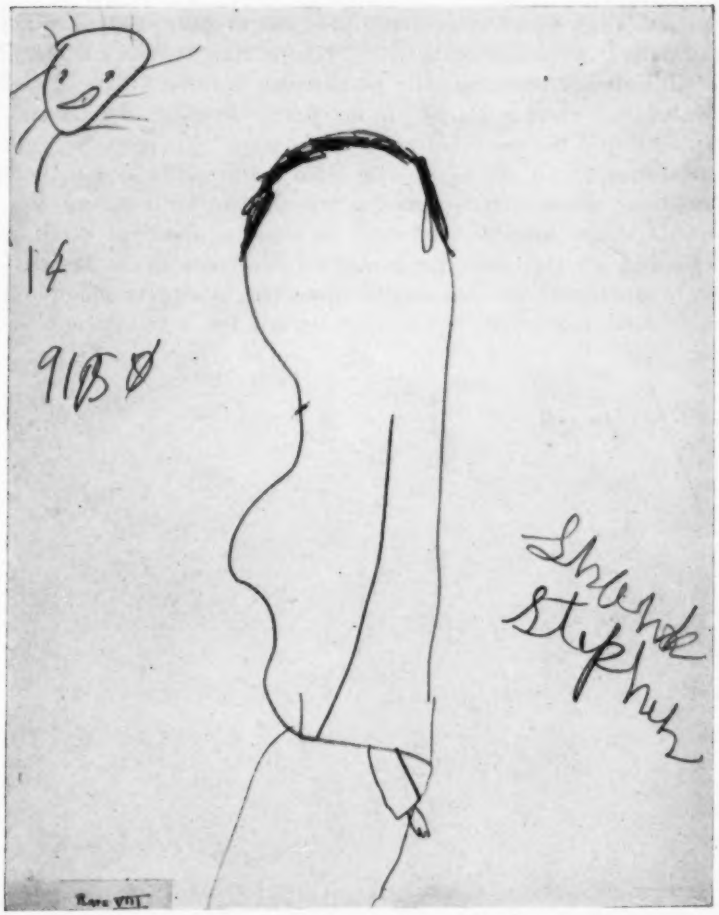

Plate VIII.—Goodenough drawing of a boy 10 years old, with brain damage due to prolonged anoxia at birth. This drawing shows the tremendous emphasis on the head seen particularly in those organic states in which perceptual problems are outstanding. Stephen feels "there's something wrong" with his head. Other features in this drawing are the small upper extremities (repressed aggression), the figure cut off at the waist (impulse control), the sun in the corner (wish for father), and the attempt to write his name and the date (reading problem).

Plate VII.—Goodenough drawing of a girl, 7 years old, with postmeasles encephalitis. (a) Neurological findings five months after onset of encephalitis: speech staccato and unintelligible, bursts of hiccoughs, increased muscle tone right lower extremity, deep reflexes increased on right, Babinski on right, patient euphoric. Goodenough drawing shows a disorganization of the body image and a pull of the figure to the right. (b) One month later. Neurological findings unchanged but mood is now normal and patient tries to overcome her difficulty with physiotherapy. Drawing shows continued disorganization, but there is effort at compensation of the muscle pull; the figure is pulled to the left as well as to the right. (c) One year after onset of illness. Speech now clear and better controlled, patient functioning at I. Q. of 92. Deep reflexes on right still increased but spasticity is questionable. The figure drawn is much better organized and muscle pulls are not striking. The drawing, however, is rigid and shows little facial expression. In (d) one and one-half years after onset, the motility problem is mastered and the girl in the drawing is now on ice skates, and the entire figure is more relaxed. This actually corresponds to her mental state. Functioning now is at I. Q. 96. This series indicates the effect of an acute organic disease on the drawing of the human figure, showing the disorganization of body image, the effect of increased muscle tone, and the efforts at compensation.

shoes and stockings on, and was unable to adjust to other children of any age. On examination, her conversation was: "Who is Mary? Where is Mary? See Mary," all endlessly repeated. Her Goodenough drawing (Plate X) reflected this problem of "where is Mary?" in the world. In effect, she has said, "See the man. Where is the man? Let me draw the man."

How schizophrenia affects an older child's drawing is seen in Sydney, a 14-year-old boy, whose terrorized mother brought him for treatment because of outbursts of violent aggression in which he set fires, destroyed furniture, and finally attempted to chop down the door of his school with an ax. He was a child of superior intelligence, but was also immature, torn by anxiety and disorganized thinking, feeling that people would point him out and were talking about him.

Plate IX.—Goodenough drawing of a girl 10 years, 6 months old with an acute toxic psychosis, following homatropine eye drops. This drawing is striking for its appearance of motion, a whirling, vortical movement. There is also emphasis upon the periphery of the body, and the trunk merely serves to hold the peripheral structures from flying apart. This is a quality of the drawings of schizophrenic children and actually this case presented a picture resembling schizophrenia.

He was extremely demanding and incapable of tolerating the frustrations which his demands must bring. His drawing of a man (Plate XI) is hardly recognized as such. He started with the tiny figures at the top of the page to the left of the midline. Then he made them a bit larger. The third attempt again grew slightly in size (midline top of page), but then he erupted in a bizarre, aggressive figure with the peripheral appendage ending in a clawlike emphasis, a questionable introjected body, and an arrow through its head. The grotesque, irrational aggression is the outstanding feature. Immediately below the figure of the man, he drew the toothed mouth with the three eyes; again the aggression

is seen, the paranoid quality and the danger of the mouth with teeth. After producing this drawing he violently crumpled the paper and dashed it to the floor.

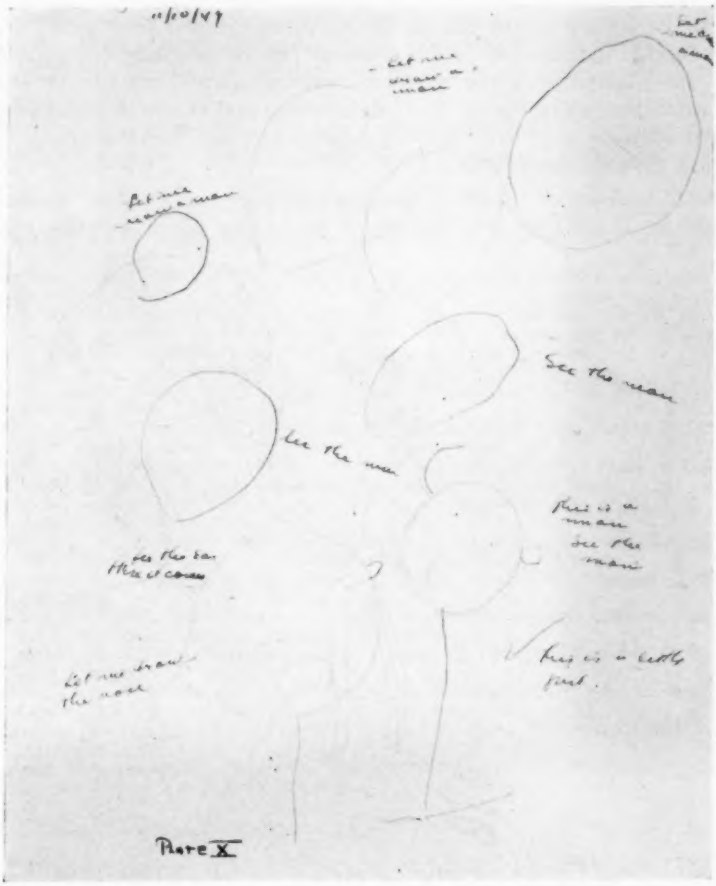

Plate X.—Goodenough drawing of a girl 5 years, 2 months old, with schizophrenia (mental age 3 years, testing minimal). The repetitive drawings here reflect her own uncertainty about just where she is in the world of space. This problem is a real one to the child with schizophrenia.

SUMMARY

Pencil and paper drawing tests, easily performed in a routine examination, offer a rapid and accurate method of estimating the developmental level of the child. These drawing tests also tend to mirror the problems of the child, physical and emotional, and so offer a clue to the patient's personality.

Tests in which the patient is asked to draw specific objects or specific patterns have been standardized. The Gesell scale, for example, places the

ability to copy a circle at about 3 years of age, the square at age 5, the diamond between 6 and 7 years of age. The Bender visual-motor Gestalt Test, in which the patient is asked to reproduce a specific series of nine geometric patterns, reveals maturational levels between the ages of 4 and 11 years.

Poor patterning of the Bender-Gestalt figures results from either organic or psychogenic disturbance. Developmental lags in language or motor fields, diffuse encephalopathy where no focal neurological findings can be elicited, reveal primitive patterning of the Gestalt figures and efforts at compensation.

Schizophrenia may show uneven functioning, and particularly, a "plasticity" of the total patterning.

The "draw-a-man" test of Goodenough gives an accurate measure of intelligence. In addition, his drawing of the human figure is really a mirror

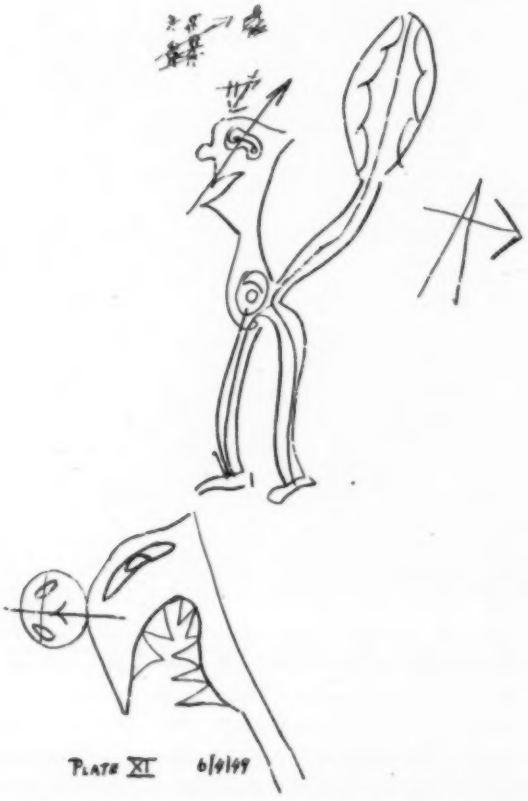

Plate XI.—Goodenough drawing of a boy 14 years, 2 months old with schizophrenia. (Mental age 17 years, 3 months.) This drawing is immediately recognized as extremely disturbed. Note the tiny figures at the top of the page to the left of the midline. This was the patient's initial response. The final figure is bizarre, aggressive, with emphasis again upon the peripheral clawlike appendage. The tiny figures are interpreted as his own overwhelming feeling of inadequacy. The toothed figure below the "man" is an aggressive mouthlike structure, the eye suggests suspicion. These interpretations fit this patient's personality.

of the patient's concept of himself. In organic states, depending of course upon the extent and location of the disease, there may be seen a disorganized figure, one with pulls from uneven muscle tone, emphasis upon perceptual structures, attempts at control of impulses.

Drawings of schizophrenic children may be markedly regressed or markedly precocious. Motion is usually seen. There is emphasis upon peripheral structures, a difficulty in placing the figure in space, bizarre figures, and sometimes introjected bodies.

Study of each whole figure reveals a dominant mood or attitude. Detailed examination shows the infinite variations which go to make the personality.

REFERENCES

1. Harms, E.: Child Art As an Aid in Diagnosis of Juvenile Neuroses, Am. J. Orthopsychiat. 11: 191, 1941.
2. Anastasi, A., and Foley, J. P.: Survey of the Literature on Artistic Behavior in the Abnormal.
   1. Historical and Theoretical Background, J. Gen. Psychol. 25: 111-142, 1941.
   2. Approaches and Interrelationships, Ann. New York Acad. Sc. 42: 1-112, 1941.
   3. Spontaneous Productions, Psychol. Monog. 52 no. 6, 1-71, 1940.
   4. Experimental Investigations, J. Gen. Psychol. 25: 177-237, 1941.
3. Bender, L., and Montaque, J. A.: Psychotherapy Through Art in a Negro Child, Coll. Art J. 1: 12-16, 1947.
4. Naumberg, M.: Drawings of an Adolescent Girl Suffering from Conversion Hysteria With Amnesia, Psychiatric Quart. 18: 197-224, 1944.
5. Alschuler, R. H., and Hattwick, LeB.: Painting and Personality: A Study of Children's Drawing, vol. 1, 2, Chicago, 1942, University of Chicago Press.
6. Gesell, A., and Amatruda, C. S.: Developmental Diagnosis, New York, 1947, P. B. Hoeber, Inc., 496 pages.
7. Bender, L.: A Visual-Motor Gestalt Test and Its Clinical Use, Research Monog. no. 3, New York, 1938, American Orthopsychiatric Association, 176 pages.
8. Wertheimer, M.: Studies in the Theory of Gestalt Psychology, Psychol. Forsch. 4: 300, 1923.
9. Schilder, P.: Mind: Perception and Thought in Their Constructive Aspects, New York, 1942, Columbia University Press, p. 142.
10. Goodenough, F. L.: Measurement of Intelligence by Drawing, Yonkers, 1926, World Book Company, 177 pages.
11. Schilder, P.: The Image and Appearance of the Human Body, Psychol. Monog. no. 4, London, 1935, Kegan Paul, Trench, Trubner & Co., Ltd., p. 11.
12. Wolff, W.: Personality of the Preschool Child, New York, 1947, Greene and Stralton, 341 pages.
13. Machover, K.: Personality Projection: in the Drawing of the Human Figure, Springfield, Ill., 1949, Charles C Thomas, 194 pages.

Comments on Current Literature

NITROGEN MUSTARD AS A THERAPEUTIC AGENT

THE beta-chloroethyl amines or nitrogen mustards were used as early as 1942 in the treatment of a variety of neoplastic diseases. The pharmacologic and experimental aspects of these substances were reviewed in considerable detail by Gilman and Philips[1] in 1946, and the initial clinical results were described about the same time by Dameshek and his associates[2] and by Jacobson and Spurr and their coworkers.[3] Since that time a considerable volume of literature has accumulated concerning the use of nitrogen mustards in the treatment of diseases of lymphatic origin.

While no malignancy has been eradicated completely by the use of these chemical agents, reports indicate that some degree of temporary control may be effected in the clinical course of many patients suffering from neoplastic disease. The form of nitrogen mustard most commonly used is methyl bis (beta-chloroethyl) amine hydrochloride or HN_2HCl. The drug affects cells in the same manner as does irradiation by roentgen-ray, and experimental studies have indicated that the biological activities of the two agents are remarkably similar.[1, 4] The exact nature of the physicochemical reactions taking place intracellularly is not clear. Some investigators have suggested that liberated hydrochloric acid may bring about protein denaturation and interfere with nuclear enzyme metabolism.[5]

Within recent months two extensive reports have appeared which analyze the effects of nitrogen mustard in the treatment of patients suffering from various neoplastic diseases. In the *American Journal of Medical Sciences* for January, 1950, Bauer and Erf[6] present the summarized results of treatment in 210 patients who received a total of 296 courses of nitrogen mustard, or 1,184 injections. These patients had a wide variety of diseases including many types of tumors and blood dyscrasias, as well as Hodgkin's disease.

Miscellaneous diseases in their series treated with nitrogen mustard included one case of myasthenia gravis and two cases of pemphigus, in none of which was there any response; one case of superior sulcus tumor in which treatment was too recent for evaluation; one patient suffering from plasmacystoma of the fifth lumbar vertebra with complete relief of pain; one patient with atopic dermatitis with itching in whom complete remission of lesions followed the treatment and in whom itching had not recurred (two months); and one patient with exfoliative dermatitis with itching who experienced complete relief after two injections.

The toxic effects of nitrogen mustard are well known, and the patients in this series of Bauer and Erf were no exception, the most common manifesta-

tions being nausea and vomiting following administration of the drug, and depression of the leucocyte count. With reference to nausea and vomiting, many patients experienced the greatest discomfort with the first dose. This finding, however, was not invariable, and no accurate evaluation could be made. In general, patients with large amounts of neoplastic tissue did not seem to suffer as severely from nausea and vomiting as did those with less extensive neoplastic involvement.

Depression of the leucocyte count was a constant finding throughout the entire series. The initial decrease in the number of lymphocytes and monocytes usually returned to normal within two to three weeks; a fairly severe neutropenia occurred with gradual drop for about two weeks and slow rise to normal level. While the depression of white blood cells was usually not sufficient for grave concern, in a few patients it was severe enough to necessitate discontinuance of the nitrogen mustard courses and institution of supportive therapy including transfusions. These authors report also a slight decrease in hemoglobin and red-cell levels following administration of nitrogen mustard.

In the series of patients reported, gastrointestinal hemorrhages occurred in six and cerebral hemorrhage in three instances. Because of the high incidence of nausea and vomiting combined with possible hemorrhage due to a disturbance in blood coagulation, particular care was exercised in the treatment of patients in the older age groups who showed evidence of arteriosclerosis with hypertension. Special care was exercised likewise in treating patients with polycythemia. One patient with polycythemia suffered a brain hemorrhage secondary to nausea and vomiting, and two others with polycythemia showed some evidence of cerebral hemorrhage. The authors point out that the possibility of this serious complication must be taken into consideration in patients with increased blood viscosity, increased blood volume, and possible cerebral arteriosclerosis.

In their discussion summary, Bauer and Erf emphasize the fact that nitrogen mustard therapy is palliative only, and stress the importance of individual variability in the response of the patient. Conditions which respond fairly well to the drug are Hodgkin's disease, fibrosarcoma, leucosarcoma, chondrosarcoma, and monocytic leucemia. Conditions which exhibit only slight change following therapy with nitrogen mustard include melanosarcoma, liposarcoma, and carcinoma with the possible exception of adenocarcinoma.

According to these authors, the use of nitrogen mustard is probably contraindicated in lymphatic and myeloid leucemia because of the severe lymphoblastic destruction. Two of their patients with Hodgkin's disease complicated by Kaposi's cell sarcoma of the lower extremities showed improvement of the Hodgkin's process following HN_2HCl treatment, but meanwhile the cell sarcoma became more extensive.

In conclusion the authors suggest that nitrogen mustard may have definite possibilities as a means of alleviating symptoms of discomfort even though the effect on the primary disease may be temporary: "carcinoma,

where it may relieve pain; polycythemia vera, where it may relieve the leg cramps due to increased blood viscosity; various dermatitides, where it may relieve itching."

An interesting clinical observation reported previously by a number of authors is described also by Bauer and Erf: the apparent sensitization of patients to roentgen-ray irradiation by nitrogen mustard. Conversely, Bauer and Erf found that patients who had become resistant to HN_2HCl, regained their sensitivity to the drug after a course of irradiation by roentgen-ray.

The March, 1950, issue of the *Annals of Internal Medicine* carries an extensive report of nitrogen mustard therapy in lymphomas and other neoplastic diseases by Alpert, Greenspan, and Peterson.[7] Fifty-two patients with various types of lymphomas and other neoplastic conditions were treated with HN_2HCl. A careful and detailed synopsis presented in tabular form includes dosage, clinical findings, blood counts, and therapeutic results.

Favorable results, although in general temporary, were obtained in twenty-seven patients suffering from Hodgkin's disease, in three suffering from giant follicular lymphoblastoma, and in two with Sternberg's disease (lympholeucosarcoma). While varying degrees of tumor shrinkage were observed in patients with lymphosarcoma, reticulum cell sarcoma, chronic lymphatic leucemia, subacute myeloid leucemia, sarcoidosis, and various types of carcinoma, no significant benefit followed the treatment. In the group of patients with Hodgkin's disease, only two were controlled for a period of more than one year by repeated courses of nitrogen mustard alone. In the majority of cases, roentgen-ray therapy was necessary for prolonged remissions.

In spite of the fact that the most significant toxic effects were observed in the hematopoietic system, panhematopenia was not, in the experience of these authors, a limiting factor in the continuance of treatment. The most serious complications encountered were thrombopenia and purpura.

According to Alpert, Greenspan, and Peterson, "nitrogen mustard therapy appeared to be most suitably indicated in the following types of Hodgkin's disease: (1) widespread involvement which could not be treated with x-ray; (2) individuals with lymphadenopathy and marked constitutional symptoms (fever, weight loss, etc.); (3) those with fever but without demonstrable enlarged nodes ('occult' febrile type); (4) patients with visceral involvement, and (5) terminal cases which had become 'resistant' to roentgen therapy." X-radiation is considered by these authors as the "therapy of choice in patients with relatively localized disease in peripheral, mediastinal, or retroperitoneal regions, with obstructive lesions about the spinal cord, biliary tract, ureters, or great vessels, with bone involvement or with fibrosing type of Hodgkin's disease."

While permanent cures of the neoplastic diseases are not to be expected by the use of the nitrogen mustards, these chemical agents seem to have wide application in a palliative capacity by bringing about temporary remissions and by contributing to the comfort of the patient. It has been suggested

that nitrogen mustard may prove of use in other conditions as a means of alleviating discomfort such as pain and itching even where there is no significant alteration in the primary disease process. If proper precautions are taken in their use, it seems reasonable to conclude that the nitrogen mustards must be regarded as useful therapeutic agents in the treatment of carefully selected patients.

RUSSELL J. BLATTNER

REFERENCES

1. Gilman, Alfred, and Philips, Frederick S.: The Biological Actions and Therapeutic Applications of the Beta Chloroethyl Amines and Sulfides, Science **103**: 409, 1946.
2. Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A., and McLennan, M. T.: Nitrogen Mustard Therapy, J. A. M. A. **132**: 126, 1946.
3. Jacobson, L. D., Spurr, C. L., Barron, E. S. G., Smith, T., Lusbaugh, C., and Dick, G. F.: Nitrogen Mustard Therapy, J. A. M. A. **132**: 263, 1946.
4. Karnofsky, D. A., Burchenal, J. J., Ormsbee, R. A., Corman, I., and Rhoads, C. P.: Experimental Observations on the Use of the Nitrogen Mustards in the Treatment of Neoplastic Disease: Approaches to Tumor Chemotherapy, Forest Ray Moulton, editor, Washington, D. C., 1947, American Association for the Advancement of Science, p. 294.
5. (a) Alpert, L. K., and Peterson, S. S.: The Use of Nitrogen Mustard in the Treatment of Lymphomata, Bull. Army Med. Dept. **7**: 187, 1947.
   (b) Barron, E. S. G., Bartlett, G. R., and Miller, Z. B.: The Effect of Nitrogen Mustards on Enzymes and Tissue Metabolism, J. Exper. Med. **87**: 489, 1948.
6. Bauer, R. D., and Erf, Lowell A.: The Clinical Effect of Nitrogen Mustard on Neoplastic Diseases, Am. J. M. Sc. **219**: 16, 1950.
7. Alpert, L. K., Greenspan, Ezra M., and Peterson, S. S.: The Treatment of the Lymphomas and Other Neoplastic Diseases With Nitrogen Mustard, Ann. Int. Med. **32**: 393, 1950.

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination in Cincinnati, Ohio, May 5, 6, and 7, 1950.

Dr. John Edward Allen, 2316 Auburncrest Ave., Cincinnati, Ohio.
Dr. Catherine Armstrong-Seward, Travis Clinic, South Ragsdale St., Jacksonville, Texas.
Dr. Samuel Harris Barron, 1951 Irving Park Rd., Chicago, Ill.
Dr. Arnold H. Becker, 124 Main St., Bristol, Conn.
Dr. Bedford Hudson Berrey, 308 South Third Street, Harlingen, Texas.
Dr. Robert Cleon Beswick, 694 Lincoln Ave., Bellevue, Pittsburgh 2, Pa.
Dr. Jack W. Bills, 117 Whittier, Idaho Falls, Idaho; presently at Children's Hospital, Cincinnati, Ohio.
Dr. Mercer C. Blanchard, 204 11th St., Columbus, Ga.
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Dr. Clifford Read Boles, 769 Yale Ave., St. Louis 5, Mo.
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Dr. Peter Carl Hoch, 858 Metropolitan Bldg., Denver, Colo.
Dr. Arthur W. Hoyt, Chickasha Hospital and Clinic, Chickasha, Okla.
Dr. Mason S. Jones, 406-12 Harries Bldg., Dayton, Ohio.
Dr. Maurice Nathaniel Kay, 183 Waterman St., Providence, R. I.
Dr. Robert Klein, Harriet Lane Home, Johns Hopkins, Baltimore, Md.
Dr. Seymour Klein, 4753 Broadway, Chicago, Ill.
Dr. William Gene Klingberg, 500 South Kingshighway, St. Louis 10, Mo.
Dr. James Abner Lauderdale, Jr., Rush Brothers Clinic, Meridian, Miss.
Dr. Katherine Cecilia Lewis, LaRabida Jackson Park Sanitarium, Chicago, Ill.
Dr. Ralph Conrad Lohrey, 628 East 185th St., Cleveland, Ohio.
Dr. Wallace Wilson Lueck, 1009 Nicollet Ave., Minneapolis, Minn.
Dr. Carl J. Marienfeld, 1819 W. Polk Street, Chicago, Ill.
Dr. David N. McClure, 7803 Clayton Rd., St. Louis 17, Mo.
Dr. William F. McGuire, 401 N. Emporia, Wichita, Kan.
Dr. Wallace Willard McCrory, New York Hospital, Rm. 819, 525 East 68th St., New York City, N. Y.
Dr. Étienne Raymond O'Brian, 101 W. 7th St., Plainfield, N. J.
Dr. Roger L. O'Toole, 410 Lafayette Bldg., Waterloo, Iowa.
Dr. Louis Penn, 1505 Grand Concourse, Bronx 52, N. Y.
Dr. Irving William Robinson, 835 West State St., Trenton, N. J.
Dr. Oliver K. Scott, 437 East 13th St., Casper, Wyo.
Dr. Robert Daniel Semsch, 1409 Willow, Minneapolis 3, Minn.
Dr. Groom Shirley Shepard, 923 Ellis Ave., Lufkin, Texas.
Dr. Flora Friedman Silberbush, 2076 East 13th St., Brooklyn 29, N. Y.
Dr. Julius Daniel Stein, 951 Park Avenue, Bridgeport, Conn.
Dr. Allan B. Stimson, 68 Arnold, New Bedford, Mass.
Dr. Ross Claud Tilbury, 544 East Kingshighway, Sherveport, La.

Dr. James L. Treadway, Jr., 710 Maison Blanche Bldg., New Orleans, La.
Dr. Robert Bruce Tudor, Quain Ramstad Clinic, Bismarck, N. D.
Dr. Selma Wehl, 1536 51st St., Brooklyn 19, N. Y.
Dr. Carl Weihl, 1008 Marion Ave., Cincinnati 29, Ohio.
Dr. Arthur D. Wolk, 69-39 Yellowstone Blvd., Forest Hills, N. Y.
Dr. Otis Wayne Yeager, 2250 Highland Ave., Birmingham 5, Ala.

At the annual meeting of the **American Pediatric Society** at French Lick, Ind., May 9, the following officers were elected for 1950-1951:

President: Dr. Bronson Crothers
Vice-President: Dr. Stanley Gibson
Secretary-Treasurer: Dr. Henry G. Poncher
Recorder and Editor: Dr. Stewart Clifford
Dr. Julian D. Boyd was elected to Member of the Council.

The following were elected to membership:

Dr. Edith Boyd
Dr. Donald E. Cassels
Dr. Sidney Gellis
Dr. Jerome Harris
Dr. Alan J. Hill
Dr. Nelson K. Ordway
Dr. Alexander Schaffer
Dr. Robert Jackson
Dr. Jerome L. Kohn
Dr. William S. Langford
Dr. Lyman Meiks
Dr. Benjamin M. Spock
Dr. Edward Pratt
Dr. Hale F. Shirley
Dr. H. E. Thelander

The **American Board of Pediatrics** announces the following dates for oral examinations:

Chicago, Ill., Oct. 13, 14, and 15, 1950.
Boston, Mass., Dec. 1, 2, and 3, 1950.

Dr. Alex J. Steigman of Cincinnati has been appointed professor of child health in the department of pediatrics at the University of Louisville.

At the May 8 meeting of **The Society for Pediatric Research,** the following officers were elected for the coming year:

President: Harry H. Gordon, Denver, Colo.
Vice-President: John M. Adams, Minneapolis, Minn.
Secretary-Treasurer: Robert Ward, New York, N. Y.

Book Review

1950 Current Therapy. Edited by Howard F. Conn, M.D., Philadelphia, W. B. Saunders Company, 736 pages. Price $10.00.

The 1949 edition was extensively reviewed in the JOURNAL last year. The new edition contains articles on therapy contributed by 229 physicians selected by an editorial board of twelve. The book contains a tremendous amount of material on "treatment" which is presented in an easily readable form. Sixteen new subjects have been included. The increasing use of the new antibiotics is amply covered.

Editor's Column

EXAMINATIONS

THE ANNUAL jamboree of examinations testing the knowledge of medical students and recent graduates which began late in April is now over. Somewhere between 1,700 and 2,000 different sets of questions were set up by the departments in the medical schools, the state licensing boards, and the National Board of Medical Examiners. A fair estimate would be about 170,000 written examinations turned in which had to be read and graded. The exact man-hours of labor employed in this task is beyond calculation. Even if a ridiculously low average of ten minutes was allotted to the reading and marking of each paper, it would take approximately a year for a team of twenty medical educators working six hours a day for five days a week to read and grade the answer papers. The task, however, could not be completed in this way, as the chances are that most of the examiners would be in a sanitarium by the end of a month.

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While everyone through personal experience is familiar with the tension and worry that goes with taking examinations, relatively few are aware of the problems and headaches of the examiners. First of all comes the question as to what the candidate at a specific level should be expected to know. Some years ago a study was made of the fourth year (final) examination in pediatrics given in twenty-odd medical schools. There was a tremendous variation in the questions asked and in the content. Perhaps the most striking thing was the way in which a number of the examinations had (subconsciously we are sure) been weighted along the line of the chief interest of the head of the department. Thus one examination would stress metabolism and chemistry and practically ignore the infectious diseases, while in another the opposite situation would be found. Many omitted the field of growth and development which forms the basis of pediatrics. We venture the thought that had some of the examinations been exchanged between schools there would have been a high mortality. Most certainly there was no unanimity of opinion shown by the examinations as to what the medical student about to be graduated should be expected to know in the field of pediatrics. A similar analysis in other fields would undoubtedly show a like situation.

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Most written examinations are set up in the time-honored "essay" form, in which in large part the candidate is asked to discuss a subject. It is an easy form when it comes to framing the questions but a tremendous chore when it comes to reading and grading. We noted a few years ago that papers read early in the morning were likely to be given higher grades than papers in the late afternoon or evening after a tiring day's work, and others have admitted the same tendency. Frequently the answer papers are divided up

and read and graded by different members of a department, which brings in the personal equation when it comes to grading. A year ago twenty papers written by fourth year students taking the National Board of Medical Examiners examination in pediatrics from each of five different medical schools were read and marked by the chief examiner. Then twenty papers from each of the same five schools were read by heads of departments in five schools in different parts of the country and the grades compared. The grades given by three department heads compared closely with the grades given by the chief examiner. On the other two, one had a much greater "spread," and the other gave grades that would have failed about one-half of the students, compared with one in twenty from the same school as marked by the chief examiner. Based on many years of experience the National Board feels that if more than 5 to 10 per cent fail an examination in the clinical subjects, the fault may lie in the examination or examiner rather than the candidates. Perhaps the questions were not fair and clear, or perhaps the examiner expected too much of the fourth year student. This matter of grading is the great problem and weakness of the "essay" type of examination. Another lies in the fact that the scope is necessarily limited. The idea, of course, is that by jumping from field to field in different years the candidate must be prepared in all, and the sampling is a satisfactory index of the candidate's general knowledge. An advantage of the "essay" type is that an experienced examiner gets a definite clue from the answers as to how well the candidate uses his knowledge. Two answers may give the same facts, but in one the material is so arranged that it is very evident that the candidate thinks straight in using his knowledge, while in the other it is obvious that the thinking is muddled.

Attempts have been made to develop a more comprehensive type of examination by the use of the "true and false" and "multiple choice" answer types of examinations. Both are difficult to set up but easy to grade. In this way the work on the part of the examiner is about the same as in the essay type—only in the one he works after the examination, in the other two before.

The fundamental weakness of the "true and false" in the opinion of many lies in the fact that so much that is of importance in clinical medicine cannot be answered categorically as true or false. Hence much must be eliminated. A second weakness is that it tends to grade only factual knowledge—the kind that can be obtained by reading a text—and gives no clue as to how a man uses the facts. It is the form of written examination used at present by the American Board of Pediatrics, and used as it is by them in conjunction with an oral examination is fairly satisfactory. It enables the Board to get a broader picture of the candidate's general knowledge than obtained by the oral examination alone.

Much better as an all-around comprehensive examination is the "multiple choice" type, in which the candidate is asked to select the correct answer out of about five choices, but it is a form that is exceedingly difficult to set up. A team of educators is required to get it underway and then constant supervision and change are necessary to keep it abreast of current knowledge. It

is at present used by the American Board of Internal Medicine as a screening examination which must be passed before a candidate is admitted to the oral examination.

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In recent years the form and content of examinations has been the subject of considerable study, and an attempt has been made to introduce a scientific approach or attitude. A group has been formed whose sole purpose or function is the giving of examinations. It now gives among others the Medical College Admission Test used by some schools in the selection of students, and the College Entrance Board examinations. The examinations follow the "multiple choice" type of question and a special pencil is used for marking the answer number selected on a special sheet of paper. The sheets are then run through a specially adapted electrical machine and the grades obtained immediately. It permits of the checking of the relative value of individual questions. The content and scope of the examination involve the use of a group of educators in each particular field, but the detailed construction of the questions is done by specialists trained and experienced in this work. Perhaps in some not too far distant day the medical schools, through some mechanism such as the National Board, will adopt an examination of this type that will be given to every student in each subject. It would not only relieve the faculties of a tremendous burden, but undoubtedly have a tremendous impact on the quality of medical pedagogy.

This discussion has been concerned with the content and grading of the written examinations. It has always been our contention that when a student fails the written examination, his laboratory or ward work through the year should be taken into consideration before the failure is made final. No written examination has as yet been devised which gives a final and complete evaluation of an individual's knowledge and ability. B. S. V.

The April 15, 1950, number of the *Journal of the American Medical Association* contains a list of approved pediatric residencies which now number 1,092 in 216 hospitals. The total number of residencies in all fields approved by the Council on Medical Education was 18,699. Of these, 1,179, or approximately 6 per cent, were reported as vacant, but only eight pediatric residencies, or less than 1 per cent of the pediatric residencies, were reported as vacant.

While some of the smaller hospitals offer a beginning stipend of $150 to over $200 per month, the larger hospitals for children, which are usually associated with a university department and which are the most sought after for training, still offer a beginning stipend of "cigarette money" as the residents term it.

It is obvious from the thousand men and women in training for pediatricians that the Board will have plenty of work to do for a number of years, and that in the near future there will be a large number of pediatricians in the United States trained to give a high type of medical care to children.